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COVID-19, immunity, and vaccination: unravelling the interplay of sex, gender, age, and the exposome

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Abstract

Sex- and gender-related differences profoundly influence immune responses to SARS-CoV-2 infection and vaccination but remain insufficiently considered in research and public health strategies. This review explores how sex, gender, age, and the exposome interact to shape susceptibility to coronavirus-19 disease (COVID-19), disease severity, Long COVID, and vaccine-induced immunity. Males experience higher rates of severe disease, hospitalisation, and mortality, whereas females generally mount stronger innate and adaptive immune responses, contributing to greater resilience. These differences arise from a complex interplay between biological factors and gender-related determinants, including occupational exposures, healthcare access, health-related behaviours, socioeconomic conditions, and the microbiota, which contribute to the individual exposome. This review also highlights the impact of ageing on SARS-CoV-2 immunity, highlighting the preserved immune regulation observed in centenarians, which may contribute to protection against severe COVID-19 despite advanced age. Current evidence on Long COVID is discussed, including its higher prevalence among females and the sex-specific immunological pathways that may underlie persistent symptoms. We examine age-, sex-, and gender-related differences in vaccine response, distinguishing efficacy from effectiveness. Although females generally mount stronger antibody responses, this advantage does not necessarily translate into greater clinical protection. The relative benefit of vaccination appears greater in males because of their higher baseline risk of severe disease. Finally, we discuss how exposomic factors, including lifestyle, microbiota composition, and environmental and social determinants, influence vaccine responsiveness and hesitancy. Integrating sex, gender, age, and the

exposome perspectives is essential for developing more equitable and personalised strategies to prevent and manage COVID-19 and future emerging diseases.

Keywords

age, COVID-19, exposome, gender, immunosenescence, Long COVID, sex, vaccination

Introduction

Since its emergence in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally at an unprecedented pace, leading the World Health Organisation (WHO) to declare coronavirus-19 disease (COVID-19) a global pandemic on March 11, 2020. SARS-CoV-2, a member of the *Betacoronavirus genus* within the Coronaviridae family, is now known to be primarily transmitted via respiratory droplets [1]. Similar to other coronaviruses affecting the respiratory tract, it targets alveolar epithelial cells in the lungs by binding to the angiotensin-converting enzyme (ACE) 2 receptor and employing the transmembrane serine protease 2 (TMPRSS2) to facilitate entry through spike protein activation.

Although many naïve individuals infected with SARS-CoV-2 experienced only mild disease, severity and mortality were notably higher among older adults, particularly males [2]. Male sex has since been recognised as a risk factor for adverse COVID-19 outcomes, as males had disproportionately higher rates of hospitalisation, intensive care unit (ICU) admission, and mortality reportedly up to threefold greater than in females [3, 4]. This sex-biased pattern aligns with broader infectious disease data, reflecting underlying biological differences shaped by sex hormones and genes located on the sex chromosomes [4–8]. Table 1 provides an overview of the fundamental pathways by which sex hormones modulate immune function, and in the next section the effects of the X chromosome are addressed. However, it is clear that independent of biological sex, gender-related social and environmental factors also play a role in disease outcome. Gender, defined as the socially constructed norms and expectations that determine the behaviours, opportunities, and roles of women, men, and gender-diverse individuals, plays an important part in shaping health outcomes. Power dynamics linked to gender, as well as to factors such as social class, ethnicity, and religion, often limit equitable access to healthcare, resources, and decision-making, thereby influencing both the delivery and use of health services [5, 6]. Furthermore, the exposome (i.e., the totality of environmental exposures, including education, socioeconomic status, and microbiota) interacts with biological and social factors throughout life to influence health and immune responses [9]. The nature and intensity of these exposures are influenced not only by biological sex but also by cultural expectations, social practices, and gender norms. Accordingly, defining and characterising the exposome with attention to both sex and gender identity may provide important insights into the determinants of individual health outcomes, including responses to infections [10].

Host genetic variation is also recognised as an important determinant of susceptibility to SARS-CoV-2 infection and disease severity. However, because the present review focuses on the interplay between sex, gender, age, and the exposome, a detailed discussion of genetic determinants is beyond its scope. Comprehensive reviews on the genetics of COVID-19 are available elsewhere [11, 12].

Although this is a narrative review, we provide a description of how the literature base was assembled. The search covered literature published from January 2023 onwards, building on evidence identified through the authors' previous work in the field, and was subsequently updated through January 2026 to incorporate the most recent publications. PubMed was searched for English-language articles, and the search was supplemented with relevant grey literature from institutional websites. Retrieved publications were screened for relevance to the scope of the review, and the reference lists of key articles, including systematic reviews and relevant guidelines, were manually examined to identify additional eligible studies. The search strategy combined the term "COVID-19" (in the title or abstract) with the keywords "sex", "gender", "exposome", "vaccine", and "vaccination", used individually or in combination. Preference was

given to original research articles, systematic reviews, and authoritative reports that addressed the influence of sex, gender, exposome-related factors, and vaccination on susceptibility to SARS-CoV-2 infection, immune responses, and COVID-19 outcomes.

Following this literature search, together with evidence derived from our previous publications, several interconnected themes emerged. With regard to SARS-CoV-2 infection, these included the influence of sex and age, the distinctive case of centenarians, the contribution of the exposome and gender, and Long COVID (LC). In relation to vaccination, the main topics were the effects of sex and age, adverse events, and the roles of gender and exposome-related factors. These themes form the basis of the individual sections of the review.

Table 1. Sex hormones regulate immune response [5, 6, 13, 14].

Hormone	Mechanism of action	General immunological effect
Oestrogen	Increases B cell proliferation, class switching to immunoglobulin (Ig) G, T helper (Th) 2 and T regulatory cell (Treg) responses; modulates Treg transcriptional programs	Immune-enhancing (not during pregnancy); promotes humoral responses
Progesterone	Induces anti-inflammatory molecules; inhibits Th1 and Th17 pathways; modulates antigen presenting cell (APC) activation	Immunosuppressive; anti-inflammatory
Testosterone	Reduces pro-inflammatory cytokines [interleukin (IL)-1β, IL-6, tumour necrosis factor (TNF)]; increases IL-10; inhibits T cell proliferation; suppresses B cells and natural killer cytotoxicity	Immunosuppressive; anti-inflammatory
Prolactin	Promotes B cell activation and antibody production; upregulates costimulatory molecules on APCs; modulates Th1/Th2 cytokines	Immune-enhancing

Oestrogens are key regulators of immune function, with effects that depend on hormonal concentration, biological context, and the pattern of receptor engagement. At low or intermediate levels, as typically observed during reproductive life and at defined stages of the menstrual cycle, oestrogens tend to strengthen innate and adaptive immune reactivity. In this setting, they can increase the release of pro-inflammatory mediators, including IL-1β, IL-6, TNF-α, and type I interferon (IFN-I). These actions are partly mediated through enhanced expression of Toll-like receptor (TLR) 7 and TLR9, increased responsiveness of plasmacytoid dendritic cells (DCs), and promotion of B-cell persistence, maturation and differentiation, together with support of Th17 polarisation [15]. In contrast, the high oestrogen concentrations reached during pregnancy are associated with a more tolerogenic immune environment. Under these conditions, immune responses are redirected towards Th2- and Treg profiles, FOXP3 expression is increased, and anti-inflammatory mediators such as IL-10 and transforming growth factor-β (TGF-β) are favoured. These changes contribute to the establishment and maintenance of immune tolerance at the maternal-foetal interface [16]. In addition, the biological effects of oestrogens are complicated by the distinct signalling properties of oestrogen receptors (ERs). ERα activation is generally linked to inflammatory immune pathways, whereas ERβ signalling is more often associated with regulatory or anti-inflammatory responses. Since the relative expression of ERα and ERβ differs among immune cell populations, tissues, and stages of life, the ERα/ERβ balance may influence both the intensity and the functional orientation of immune responses [17]. Overall, these observations indicate that oestrogens may initially amplify immune activation, thereby supporting effective pathogen control, while later favour regulatory mechanisms that limit prolonged or excessive inflammation. Alterations in this dynamic equilibrium may help explain the greater predisposition of females to several inflammatory and immune-mediated disorders. Adapted from [8] under a Creative Commons CC-BY license.

Response to SARS-CoV-2 infection: role of sex and age

The X chromosome is particularly enriched in immune-related genes and regulatory elements that orchestrate both innate and adaptive immune responses. Many diseases show a pronounced sex bias, which, beyond hormonal and socio-behavioural factors, is driven by X-linked genes and the regulation of X-chromosome inactivation (XCI). Because XCI makes females functional mosaics for X-linked gene expression, variability in this process, such as skewed inactivation or the escape of specific genes from silencing, may confer an immunological advantage in the context of infectious diseases. Notably, approximately 15–30% of genes on the inactive X can partially escape silencing, depending on cell type, age, and genetic background. While some genes consistently evade XCI, others do so in a context-dependent manner, potentially enhancing immune responsiveness in females. Emerging evidence further indicates that in activated immune cells, particularly B and T lymphocytes, XCI control may be relaxed, allowing selective reactivation of X-linked genes. Among the most relevant are Toll-like receptor (TLR) 7 and TLR8, highly expressed in human plasmacytoid dendritic cells (DCs) and key regulators of $CD8^+$ T-cell responses, T helper 1 (Th1)/Th17 differentiation, and B-cell activation. Accordingly, differences in X-chromosome dosage and inactivation patterns may also influence T regulatory cell (Treg) biology in females [5, 6, 18–20].

A key unresolved question remains whether sex differences in immunity are primarily driven by sex chromosome complement, by sex hormones, or a context-dependent interaction between the two. For example, a recent in vivo study [21] demonstrated a functional synergy between X-chromosome dosage and oestradiol in regulating memory B cells (Table 2).

Table 2. Interaction between sex chromosomes and oestradiol in the regulation of memory B cells.

Sex chromosomes	Oestrogen levels	Population	Frequency of memory B cells class-switched	Immunological effect
XX	High	Post-puberty and pre-menopausal cisgender women	Higher	Enhancement of humoral immune memory
XX	High	Postmenopausal cisgender women on HRT	Higher	Restoring memory compartment B
XY	High	Transgender women (XY) on oestrogen therapy	Not significantly increased	Oestrogen is insufficient in the absence of a double X chromosome
XX	Low	Pre-puberty and post-menopausal cisgender women	Lower	Reduction in immune memory
XX	Low	Transgender men (XX) with pubertal blockers ± testosterone	Lower	Oestrogen dependence in the XX context
XY	Low	Pre- or post-puberty cisgender men	Lower	Immune profile is less oriented towards antibody response
XY	Low	Transgender women (XY) with puberty blockers	Lower	Absence of effective oestrogenic stimulation

After puberty, sex-related differences emerge in the memory B-cell compartment, with cisgender women (assigned female at birth) showing higher frequencies than age-matched cisgender men. As these cells are essential for long-term humoral immunity and rapid antibody responses upon antigen re-exposure, this difference may have functional relevance. The attenuation of this difference after menopause points to an important hormonal contribution. This interpretation is further supported by observations in transgender individuals: suppression of endogenous oestrogens in transgender men with an XX chromosomal complement was accompanied by a reduction in memory B-cell frequencies, whereas oestrogen administration to transgender women with an XY karyotype did not induce a comparable increase. A similar pattern has been reported in postmenopausal women, in whom hormone replacement therapy (HRT) was associated with higher memory B-cell counts than in untreated counterparts [21]. Reprinted from [22] under a Creative Commons CC-BY license.

Mosaic loss of the Y chromosome (mLOY) is a common age-associated somatic alteration in males, with a prevalence approaching 40% in individuals older than 70 years. This phenomenon involves the progressive accumulation of hematopoietic cells lacking the Y chromosome. When such chromosomal losses occur in somatic stem or progenitor cells, they propagate in a mosaic pattern, affecting descendant cell lineages while remaining absent from cells derived from unaffected stem cells. Accumulating evidence indicates that LOY is associated with increased all-cause mortality and a higher risk of multiple age-related diseases. Moreover, LOY has been linked to substantial immune dysregulation, influencing systemic immune homeostasis as well as cell-type-specific responses across a range of pathological contexts, including infectious diseases such as COVID-19 [23, 24].

Following the initial steps of viral entry after binding ACE2, and before the activation of the adaptive immune response against SARS-CoV-2, the innate immune system plays a crucial role by detecting viral RNA, primarily via TLR7, which in turn initiates the production of type I interferon (IFN-I). Theoretically, sex differences may already play a role at this stage [1]. The *ACE2* gene, which is itself located on the X chromosome, is subject to modulation by oestrogens, leading to its reduced expression, whereas TMPRSS2 expression is influenced by androgen receptor signalling. Moreover, for the reasons outlined above, females tend to exhibit higher expression of TLR7 in immune cells, resulting in enhanced IFN-I production upon receptor activation. Nonetheless, the exact contribution of ACE2 and TMPRSS2 to the sex-based disparities observed in COVID-19 outcomes remains incompletely understood [1, 6, 25, 26]. In one study, a specific ACE2 variant has been associated with a reduced susceptibility to SARS-CoV-2 infection, though it does not appear to influence disease severity; notably, these findings did not account for potential sex-based differences [27]. Intriguingly, elevated ACE2 levels are linked to better COVID-19 outcomes by converting toxic angiotensin II to angiotensin-(1–7), mitigating severe cardiopulmonary injury. Although ACE2 facilitates viral entry, its protective role in the renin-angiotensin-aldosterone system pathway helps

counteract the damage caused by the virus, especially in patients with comorbidities [28]. Regarding TMPRSS2, its expression is mediated by androgen receptor signalling and may therefore also represent one of the contributing factors to the increased severity of COVID-19 observed in males compared to females [6]. Additionally, genetic variants in androgen receptors located near the *TMPRSS2* gene have been linked to worse clinical outcomes in specific male populations where these mutations are more common, raising the possibility that androgen deprivation therapy could mitigate disease severity in such cases [29].

Irrespective of the considerations outlined in the preceding paragraph, immune ageing plays a significant role in the onset and progression of COVID-19 [30]. In older people, alterations in innate immune responses, particularly in the number of DCs [31], along with impaired adaptive immunity and a heightened pro-inflammatory response, may impair effective viral clearance and contribute to the excessive inflammatory responses characteristic of cytokine storms in severe cases [1, 6, 32]. Indeed, "inflamm-ageing", a hallmark of the ageing immune system in industrialised populations [33], is characterised by increased production of pro-inflammatory cytokines, acute-phase proteins, and oxidative stress, as well as reduced levels of anti-inflammatory cytokines [6, 32]. This chronic pro-inflammatory state may exacerbate the virus-induced cytokine storm, responsible for severe lung disease in COVID-19 patients [30, 34]. Age-related alterations in both innate and adaptive immunity, which also exhibit sex-specific patterns [5, 6], may therefore help explain the observed differences in COVID-19 severity and mortality across age groups and between sexes. SARS-CoV-2 was a newly emerging pathogen to which people had never been previously exposed. As a result, the first step in the adaptive immune response is its recognition by naïve lymphocytes. In older patients, the reduced number of peripheral naïve T cells results in a failure to mount strong protective immunity against the virus [32], although adequate protective responses after appropriate vaccination document that the older immune system is intrinsically capable of clinically protective responses [35]. The state of immune ageing can hinder the development of optimal primary immune responses to the virus [6, 30]. Moreover, the distribution of lymphocyte subsets changes with age in a sex-specific manner [1, 36], further contributing to the observed sex differences in the response to SARS-CoV-2. An epigenetic study by Márquez et al. [37] revealed greater genomic activity in B and T cells in older females, suggesting a more pronounced age-related decline in T-cell populations in males.

In older males with COVID-19, mLOY has been found to be strongly associated with increased mortality. This chromosomal alteration contributes to immune impairment, weakening the initial defence against SARS-CoV-2 and consequently increasing the risk of severe disease progression. mLOY primarily affects granulocytes and monocytes, correlating positively with disease severity, fatal outcomes during intensive care, and pre-existing vascular conditions. Dysfunctional immune cell activity linked to mLOY reduces the efficiency of antiviral responses and may partially account for the observed sex-based differences, as well as the higher mortality rates among older males with COVID-19 [24]; older males, particularly those with one or more comorbidities, appear to be among the most vulnerable groups, although some studies have shown that the increased risk associated with male sex persists independently of comorbidities [1].

Lastly, it is important to consider the findings from a study that analysed sex differences in excess mortality across 27 European countries from the 2016/2017 to 2019/2020 seasons [38]. The study reveals that during periods of excess mortality, particularly the winter peaks associated with respiratory pathogens, males experience a disproportionately greater increase in mortality compared with females. This trend was observed to a similar degree during both influenza epidemics and the SARS-CoV-2 pandemic. Consequently, these findings suggest that the sex disparities observed in COVID-19 mortality are not unique to this pandemic but rather reflect a broader and consistent pattern seen across infectious diseases, especially those affecting the respiratory system. Consistent with this, data from diverse countries and cultural contexts throughout the COVID-19 pandemic have shown that severe disease occurs more frequently in males than in females. Male patients were approximately twice as likely to require ICU admission and had about a 30% higher risk of COVID-19-related mortality compared with female patients [39].

Figure 1 summarizes sex-related differences in immune responses to SARS-CoV-2 infection.

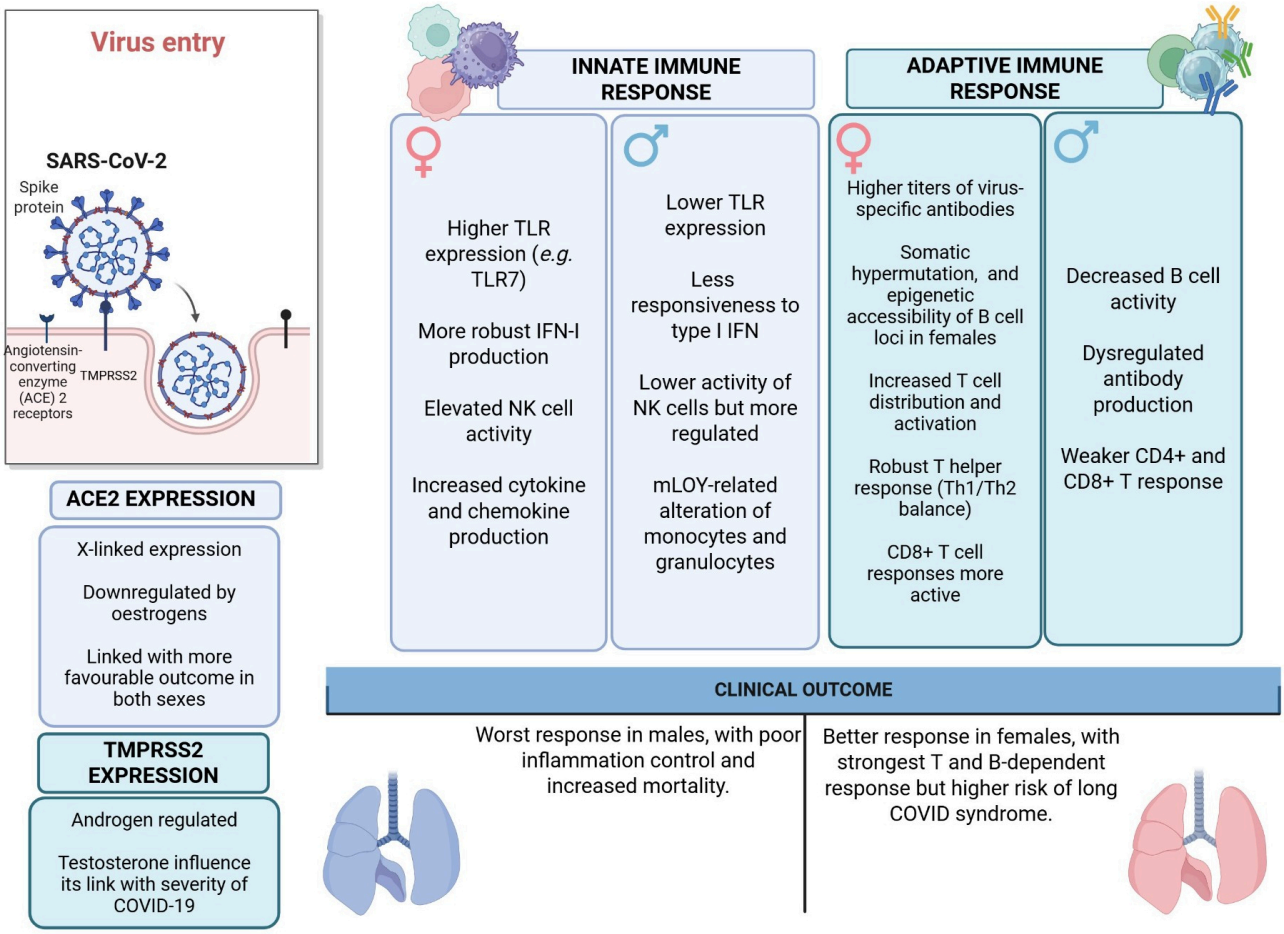

Figure 1. Sex-related differences in immune responses to SARS-CoV-2 infection. Schematic representation of sex-specific mechanisms influencing SARS-CoV-2 entry, innate and adaptive immune responses, and clinical outcomes. Viral entry is mediated by ACE2 and TMPRSS2, whose expression is modulated by sex hormones and genetic factors (including X-linked regulation). Females exhibit stronger innate immune responses, characterized by higher Toll-like receptor expression (e.g., TLR7), enhanced type I IFN production, and increased natural killer (NK) cell activity, whereas males show reduced TLR signalling and interferon responsiveness as well as dysfunctional monocytes and granulocytes due to mosaic loss of the mLOY. In the adaptive arm, females develop higher titers of virus-specific antibodies and more robust T- and B-cell responses, while males display weaker humoral and cellular immunity. These differences contribute to sex-biased clinical outcomes, with higher severity and mortality in males and stronger immune responses, but increased risk of Long COVID in females. References in the text. Created in BioRender. Calabrò, A. (2026) https://BioRender.com/dn9fleg.

Response to SARS-CoV-2 infection: the case of centenarians

A recent narrative review [1] re-examined the influence of age and sex on COVID-19 mortality, reaffirming that females generally exhibit greater resilience to the disease. This observation is consistent with broader evidence showing that females tend to outlive males, even under extreme conditions such as famines and epidemics [40]. While centenarians, in general, do not appear to have a lower mortality rate than other older populations, likely due to their frailty, an interesting finding emerged during the first pandemic wave in 2020. Centenarians over the age of 101 (born before 1919), but not “younger” centenarians, appeared to be more resilient to COVID-19 [41, 42]. This resilience has been hypothesised to be associated with prior exposure to the 1918 Spanish influenza pandemic, although the underlying biological mechanisms remain poorly understood and largely speculative. To explore whether the capacity of older centenarians to withstand SARS-CoV-2 infection could be connected to their prior experience with the Spanish flu, a retrospective serological study was conducted [43]. The study assessed neutralising antibodies in serological specimens from 33 centenarians, including 11 semi- and super-centenarians, born between 1905 and 1922, evaluating their reactivity against both SARS-CoV-2 and the 1918 H1N1 influenza virus. Clinical history as well as laboratory findings, such as antibodies targeting the virus nucleocapsid protein,

revealed that eight centenarians had been infected with SARS-CoV-2. Despite the advanced age of 3 of these individuals (between 109 and 110 years old), their infections were either asymptomatic or mild, and none required hospitalisation. Importantly, the neutralising anti-spike antibody levels observed in these infected or vaccinated centenarians exceeded those measured in a control group of randomly selected individuals aged around seventy. This suggests that older centenarians possess a remarkable resilience to COVID-19, demonstrating the ability to generate high titres of neutralising antibodies while experiencing only mild or asymptomatic disease. Furthermore, all centenarians exhibited antibody levels against the 1918 H1N1 virus that were significantly elevated, nearly 50-fold higher, compared to those in the seventy-year-old control group. Notably, centenarians whose blood samples were collected prior to the pandemic tested negative for SARS-CoV-2 but possessed neutralising antibodies targeting the 1918 H1N1 virus. This rules out the possibility of cross-reactive antibodies [43]. Rather, these findings are consistent with the hypothesis that early-life exposure may act as a selective pressure, favouring the survival of individuals with a more robust immune system. Likewise, another study reported that three Brazilian supercentenarians survived SARS-CoV-2 infection in 2020 prior to the availability of vaccination. Despite their extreme age, they exhibited robust SARS-CoV-2-specific immunoglobulin G (IgG) and neutralising antibody responses, along with enrichment of plasma proteins and metabolites associated with innate immune responses and host defence pathways. Together, these findings suggest that resilience to COVID-19 in these individuals may reflect a combination of genetic background and preserved functionality of both innate and adaptive immune compartments [44].

Thus, the resilience to COVID-19 observed in the oldest centenarians appears to be more closely related to effective regulation of immune-inflammatory responses, potentially distinguishing them from younger centenarians [45, 46]. Indeed, increasing evidence suggests that immune ageing in this population should not be interpreted as a uniform decline, but rather as a process of selective and differential adaptation. For instance, expansions of terminally differentiated effector memory T cells, including γδ and $CD8^+$ subsets, together with an elevated number of natural killer (NK) cells and a shift toward a T-cell-dominated immune profile, may represent an adaptive reconfiguration rather than immune exhaustion [47–50]. Moreover, using single-cell transcriptomic analyses, a unique population of cytotoxic $CD4^+$ T cells characterised by the acquisition of functions typically attributed to $CD8^+$ T cells has been described. These cells produce IFN-γ and tumour necrosis factor (TNF)-α, thereby sustaining potent cytotoxic and antiviral activity [51]. Unfortunately, in these studies, a sex-stratified analysis was not feasible, as the majority of the oldest centenarians were females [52].

Taken together, these findings suggest that centenarians, particularly the oldest centenarians, represent a valuable human model for investigating how immunosenescence, biological sex, and exposomic factors interact to promote immune resilience against COVID-19 and other emerging infectious diseases.

Response to SARS-CoV-2 infection: role of exposome and gender

Although sex is an important determinant of immune function, gender introduces an additional level of complexity. Gender refers to the social and cultural roles, behaviours, and expectations associated with being perceived as a man or woman, which can significantly influence health outcomes. These gender-related factors encompass social determinants that may affect the likelihood of viral exposure, patterns of healthcare seeking, access to medical services, disease reporting, and decisions regarding treatment or preventive interventions. Cultural contexts may further shape these dynamics, sometimes leading to inconsistent or even contradictory findings on gender-related differences in infections across different regions of the world [39, 53].

As highlighted in this review, most available data indicate a higher incidence of severe COVID-19 and mortality among males. However, infection rates by sex vary across populations and are influenced by socioeconomic and cultural factors that shape gender roles. For example, women's apparent resilience to COVID-19 may be underestimated in low- and middle-income countries (LMICs), where they often face more limited access to healthcare than men. This disparity may distort epidemiological findings and lead to inaccurate conclusions regarding sex-associated differences in infection rates [29].

Multiple factors, including host genetics, SARS-CoV-2 variant, age, sex, gender, and pre-existing comorbidities, influence both susceptibility to SARS-CoV-2 infection and the severity of COVID-19. These include several aspects of the exposome, such as lifestyle behaviours, diet, physical activity, smoking, and substance abuse, as well as socioeconomic variables, including educational attainment, access to reliable health information, and availability of healthcare services, collectively referred to as the social determinants of health. Environmental exposures, including xenobiotics and other pathogens, also contribute, along with genetic variations that influence immune responses [9, 10, 54, 55].

A comprehensive review [56] examined how the exposome, particularly social determinants of health, socioeconomic status, and adverse neighbourhood environments, may contribute to disproportionate COVID-19 severity and mortality through immune system dysregulation. The authors reported that individuals exposed to chronic social adversity often display persistent low-grade inflammation and altered immune profiles characterised by dysregulated NK cells, monocytes/macrophages, and increased levels of pro-inflammatory cytokines such as IL-6. These immune alterations, driven by factors including chronic psychosocial stress, discrimination, and environmental deprivation, may predispose the immune system to exaggerated inflammatory responses following SARS-CoV-2 infection, thereby exacerbating disease severity. Importantly, IL-6 appears to act as a key molecular mediator linking social adversity to both chronic diseases and severe COVID-19 outcomes through its role in systemic inflammation and cytokine storm syndromes. The review further emphasised the need for mechanistic studies investigating how specific social and environmental stressors influence immune signalling pathways. It also highlighted the importance of integrated public health strategies that address upstream social inequities alongside biological interventions such as IL-6-targeting therapies. Unfortunately, sex and gender variables were not included in the analyses considered in that review [56].

A recent population-based study, which did consider sex, examined how socioeconomic deprivation, seasonality, and restrictive public health measures jointly influenced the local spread of COVID-19 in Southern Italy. Higher deprivation was associated with greater incidence, particularly during autumn and winter seasons and under less stringent public health restrictions. Although sex was included as a covariate in the analysis, only a minimal difference was observed, with males showing a slightly higher estimated incidence than females [57]. The global impact of SARS-CoV-2 has also been associated with several urban environmental factors, particularly exposure to air pollution. A recent systematic review and meta-analysis assessed multiple studies to evaluate how urban characteristics influence COVID-19-related health outcomes. The analysis suggested that several components of the urban exposome significantly influenced pandemic severity and outcomes. Among these, urbanisation and elevated levels of ambient air pollution, especially exposure to fine particulate matter ($PM_{2.5}$), emerged as major contributors. These findings highlight the need for further research on how combinations of urban exposures influence COVID-19 outcomes, while accounting for individual factors such as sex and other health-related variables [55].

In this context, a recent study [58] investigated variations in excess mortality during the COVID-19 pandemic across countries, stratified by sex and age, and examined their association with national income levels. The analysis relied on WHO estimates of excess mortality disaggregated by sex and age and included only countries with available data on all-cause mortality. To explore cross-national patterns, the researchers used country-specific Poisson regression models, employing excess death counts by sex and age group as the primary units of analysis. The results confirmed that males experienced higher mortality rates than females in nearly all countries and across all age groups above 45 years. In 2020, the pandemic significantly widened the global sex gap in mortality, although the magnitude of this disparity varied across countries and was influenced by national income levels. In high-income countries (HICs), excess mortality was substantially lower among females than males. In contrast, in LMICs, the sex ratio in excess mortality closely resembled the expected sex ratio for all-cause mortality. Interestingly, in HICs, the sex disparity in excess mortality observed in 2020 diminished in 2021. Overall, although the COVID-19 pandemic disproportionately affected males in terms of mortality, the magnitude of this sex difference varied according to national economic status. These differences likely reflect cross-national variations in infection

rates and infection fatality ratios between the sexes. The narrowing of the sex mortality gap observed in HICs in 2021 was probably related to the rapid and widespread implementation of vaccination campaigns.

The findings reported by Tadiri et al. [3] further highlight the complex relationship between gender inequality and health outcomes during the COVID-19 pandemic. The observed positive association between institutionalised gender inequality and the male-to-female ratio of reported COVID-19 cases suggests that in countries with greater gender disparities, men may be disproportionately affected by the virus. Several mechanisms could explain this relationship, including differences in health-seeking behaviour, occupational exposure, and social norms influencing responses to health crises. Institutionalised gender inequalities and deeply rooted cultural norms may shape both the likelihood of exposure to SARS-CoV-2 and access to diagnostic services. For instance, men may be more likely to engage in risk-prone behaviours or to work in occupations with higher exposure risk, whereas women, despite often showing greater health awareness, may face barriers to obtaining adequate medical care. In addition, healthcare providers may sometimes underestimate women's symptoms or attribute them to psychosomatic causes, potentially delaying appropriate diagnosis and treatment. Further research is needed to better understand how cultural norms and institutional practices influence health outcomes during pandemics [6]. In particular, studies examining gender-related differences in behaviours such as mask use, social distancing, and healthcare utilisation could provide important insights. Cross-national analyses would also help clarify how varying levels of gender inequality influence COVID-19 outcomes. Such knowledge would allow public health interventions to be more effectively tailored to the needs and vulnerabilities of different populations, thereby promoting more equitable health outcomes during future health emergencies [3].

Social and cultural factors interact closely with biological sex in shaping disparities in infection risk and disease outcomes. Relevant determinants include employment patterns and occupational exposure to SARS-CoV-2. Evidence suggests that in HICs, women may be diagnosed more frequently than men, potentially reflecting greater access to healthcare services. However, this pattern may not apply in LMICs, where gender disparities in healthcare access are more pronounced. Structural factors, such as access to remote work, also influence infection risk, as the possibility to work from home can reduce exposure during a pandemic. These opportunities, however, are unevenly distributed across countries and between men and women.

Residence in long-term care facilities represents another important factor influencing COVID-19 risk. In HICs, older adults, particularly women, are more likely to reside in such facilities compared with individuals in LMICs. When these institutions operate with inadequate standards or insufficient infection control measures, the risk of viral transmission among residents increases substantially. The prevalence and distribution of pre-existing health conditions also play a critical role. For example, in many LMICs, obesity is more prevalent among women than men, a pattern that differs from that observed in many HICs [59–61].

Obesity and unhealthy lifestyles can impair immune function and increase the risk of severe infectious diseases, including COVID-19 [62]. Conversely, males have a higher prevalence of comorbidities associated with severe COVID-19 outcomes, such as cardiovascular disease, hypertension, and diabetes. These conditions are partly influenced by gender-related behaviours, as men are generally more likely to engage in risk behaviours such as smoking and heavy alcohol consumption and may experience different patterns of healthcare access across the lifespan [63].

Thus, gender may influence not only viral exposure and the previously discussed determinants but also the immune response to infection. Lifestyle factors, including alcohol consumption, smoking habits, occupational exposures, and physical activity levels, often differ between men and women and may affect immune function over time. Socioeconomic conditions and dietary patterns further contribute to these differences. In low-income settings, women may be particularly vulnerable to malnutrition and micronutrient deficiencies, which can compromise immune competence later in life [39, 53].

In conclusion, understanding the impact of gender and the exposome on COVID-19 requires moving beyond purely biological explanations to consider the complex interactions among social, environmental, and biological determinants. Among these factors, the gut microbiota represents an additional exposomic element capable of modulating immune responses, as quantitatively demonstrated in studies of vaccine responsiveness [64].

The human microbiota consists of complex microbial communities that inhabit multiple body sites, including the skin, gastrointestinal tract, oral cavity, and genital tract. The composition of these microbial ecosystems varies according to both sex and age. For instance, physiological changes occurring before and after menopause can substantially modify the vaginal microbiome, while hormonal changes during puberty contribute to the development of sex-specific microbial profiles.

A recent review [65] summarised evidence from human and animal studies showing that gut microbiota develops along sex-specific trajectories from early life, with differences in composition and alpha diversity. Alpha diversity reflects within-community richness and evenness; higher values are generally associated with greater resilience and functional balance, whereas lower diversity is often linked to dysbiosis. Sex-related differences have been reported in the abundance of major bacterial phyla from early life onwards. Boys may show a higher Bacteroidetes-to-Firmicutes ratio than girls, possibly reflecting the influence of testosterone during the early postnatal surge and puberty. In adulthood, males and females continue to differ in several microbial taxa, suggesting that circulating sex hormones help shape the gut microbiota. Experimental evidence supports this interpretation. In animal models, castration of male mice leads to gut microbial profiles that resemble those observed in females, indicating a regulatory role of male sex hormones in microbiota composition [65]. Importantly, the gut microbiota plays a critical role in modulating host immune responses, including those elicited by vaccination. Microbial-derived metabolites and microbial-associated molecular patterns can influence both innate and adaptive immune pathways, thereby shaping responses to both infection and vaccination. Consequently, sex-related differences in microbiota composition may represent an additional biological mechanism contributing to the well-documented sex differences in immune responses. However, in humans, the interpretation of these relationships is complicated by gender-related factors, such as diet, lifestyle, and behavioural patterns, which may also influence microbiota composition [66–69] and immune function and are largely absent in controlled animal studies. In addition, microorganisms are capable of converting inactive sex hormones into biologically active forms through enzymatic processes involving hydroxysteroid dehydrogenases. Disruption of microbial populations, such as that caused by antibiotic treatment, may impair this microbiota-mediated hormone metabolism. As a result, the levels of active circulating sex hormones may decrease, potentially influencing immune responses [70–72]. The microbiota appears to contribute to immune development, while the immune system, in turn, might influence microbial composition. This bidirectional interaction is thought to be important for maintaining homeostasis, limiting pathogen invasion, and modulating immune function. Overall, the microbiota-immune system axis might play an important role in immune maturation and in promoting a potentially beneficial microbial balance that, in turn, could support immune responses [73].

The microbiota supports immune development, while the immune system, in turn, shapes microbial composition. This bidirectional interaction is essential for maintaining homeostasis, preventing pathogen invasion, and regulating immune function. Overall, the microbiota-immune system axis plays a key role in immune maturation and in promoting a beneficial microbial balance that, in turn, supports immune response [70].

Response to SARS-CoV-2 infection: Long COVID

LC was first recognised in 2020, when patients began reporting a constellation of symptoms persisting well beyond the acute phase of infection, including cognitive dysfunction (“brain fog”), profound fatigue, dyspnoea, and chronic pain. Epidemiological data suggest that approximately 7–8% of adults experience symptoms lasting longer than three months after infection, often in the absence of a clear pathophysiological explanation. The phenomenon of LC has attracted considerable attention, particularly

regarding sex-based differences, as females appear more likely than males to experience LC, prompting investigations into the underlying biological mechanisms [74, 75]. Thus, females are approximately twice as likely as males to develop LC; however, this increased risk is not observed in older adults. This observation has led to the hypothesis that LC may be linked to autoimmune mechanisms. In this context, the condition might arise not only from organ damage caused by an excessive virus-induced inflammatory response but also from an autoimmune reaction "unmasked" by viral infection, possibly through molecular mimicry between viral antigens and host tissues [76]. This hypothesis might help explain the higher incidence of LC in females, who are generally more prone to autoimmune disorders [22, 77]. However, findings from the study discussed below [75] do not support a disease process predominantly driven by autoantibodies. A possible contribution of autoreactive T cells to LC pathogenesis could not be excluded, but current evidence remains insufficient and further investigation is needed.

It has been shown [75] that individuals with LC display persistent alterations in immune and endocrine function compared with both individuals who have fully recovered from acute SARS-CoV-2 infection and those who have never been infected. Notably, this study was among the first to identify circulating blood biomarkers capable of distinguishing LC patients with high accuracy, representing a key step toward developing reliable diagnostic tests for this condition. The investigators analysed 271 participants stratified into three groups: individuals with no history of SARS-CoV-2 infection; individuals who had fully recovered after clinically confirmed acute COVID-19; and individuals experiencing persistent LC symptoms for at least four months after confirmed infection (median duration: 12 months). Exploratory analyses revealed significant, long-lasting immunological differences between LC patients and demographically matched control groups more than one year after the acute infection. Marked alterations were observed in circulating immune cell compartments. LC was associated with increased frequencies of non-classical monocytes, double-negative B cells, and $CD4^+$ T cells producing IL-4 and IL-6. These changes correlated with immune reactivity to lytic Epstein-Barr Virus (EBV) antigens but not to SARS-CoV-2 antigens. In contrast, conventional type 1 DCs and central memory $CD4^+$ T cells were reduced, whereas the absolute number of exhausted $CD4^+$ T cells was increased. Upon in vitro stimulation, T cells from LC patients produced significantly higher levels of intracellular IL-2 ($CD4^+$ and $CD8^+$ T cells), IL-4 ($CD4^+$ T cells), and IL-6 ($CD8^+$ T cells). Collectively, these findings are consistent with a Th2-skewed $CD4^+$ T-cell activation profile, potentially driven by EBV reactivation. In parallel, LC patients displayed elevated antibody titres against SARS-CoV-2, EBV, and varicella-zoster virus antigens. Pronounced differences were also observed in circulating cytokines and hormones, particularly cortisol. Using unbiased machine-learning approaches, a core set of immunological and hormonal features was identified that robustly predicted LC status, highlighting candidate pathways and biomarkers for future validation and clinical application [75].

A separate study employing multi-omics analyses sought to further elucidate the mechanisms underlying LC [78]. Peripheral blood samples from a prospective cohort were profiled during acute severe SARS-CoV-2 infection and at 3- and 12-month follow-up in 45 individuals who either developed LC or fully recovered. The analyses revealed sex-dependent immune pathways associated with LC development. Among males who developed LC, acute infection was characterised by enhanced transforming growth factor-β (TGF-β) signalling, a strongly immunosuppressive pathway. In contrast, females who later developed LC showed reduced TGF-β1 expression during the acute phase and increased expression of genes escaping XCI during acute infection compared with females who recovered. In addition to these sex-specific differences, several immunological alterations were shared between males and females with LC. These included changes in monocyte phenotype and activation status, as well as widespread up-regulation of nuclear factor-κB transcriptional programmes across multiple immune cell types during both acute disease and convalescence. Individuals with persistent LC symptoms displayed reduced expression of ETS1 (E26 transformation-specific 1 of the ETS family of transcription factors involved in gene regulation) across lymphocyte subsets, accompanied by increased intracellular IL-4 production in T-cell populations. This pattern suggests that dysregulation of ETS1 may contribute to aberrant skewing toward Th2-like immune responses in LC [76].

In a prospective analysis [79] of the NIH RECOVER-Adult cohort [80], sex emerged as a significant determinant of LC susceptibility, with females at higher risk than males. Importantly, this association was context-dependent, varying according to age, pregnancy status, and menopausal stage. Stratification by age showed the greatest excess risk among females aged 40–54 years, followed by those aged 55 years and older. However, menopausal females aged 40–54 years did not exhibit a statistically significant increase in LC risk compared with age-matched males. In contrast, among non-pregnant females, elevated oestrogen concentrations combined with relatively lower testosterone levels were associated with a greater likelihood of developing LC [79].

Collectively, these studies suggest that LC may be associated with a range of innate and adaptive immune signatures, some of which appear to differ by sex. Although these findings require further validation, they may help inform the future development of more individualised therapeutic approaches, not only for LC but also for other post-viral syndromes.

Another recent study [81] investigated the role of innate immunity in LC by assessing neuroinflammation using positron emission tomography targeting the translocator protein (TSPO), a mitochondrial protein upregulated in activated microglia and widely used as an in vivo marker of neuroinflammation. The study compared patients with LC, healthy controls, and patients with multiple sclerosis, who, as expected, exhibited significantly higher TSPO uptake, consistent with the marked neuroinflammation characteristics of this disease. Overall, no evidence of widespread neuroinflammation was found in patients with LC compared with healthy controls. However, participants assessed within 16 months of SARS-CoV-2 infection showed greater white matter inflammatory activity than those with longer disease duration, suggesting that neuroinflammation may gradually resolve over time. Moreover, increased TSPO uptake in limbic regions, including the hippocampus, amygdala, and thalamus, was associated with poorer quality of life and more severe symptoms of anxiety and depression. Collectively, these findings indicate that, although persistent diffuse neuroinflammation is unlikely to be a hallmark of LC, transient inflammatory changes and limbic dysfunction may contribute to the neurological and neuropsychiatric symptoms observed in a subset of patients [81].

Finally, the exposome may also contribute to LC susceptibility. In a population-based prospective birth cohort, residential exposure to ambient air pollutants, including $PM_{2.5}$, PM_{10}, black carbon, and nitrogen oxides, was evaluated in relation to subsequent LC development during both early life and more recent periods preceding the COVID-19 pandemic. Mean annual $PM_{2.5}$ concentrations in 2019 were significantly associated with an increased likelihood of LC, particularly among individuals with pre-existing asthma and those infected with SARS-CoV-2 in 2020, compared with infections occurring in 2021. No significant interaction with sex was observed. Overall, these findings suggest that chronic exposure to air pollution may contribute to LC susceptibility, highlighting broader health consequences of environmental pollution independent of sex [82]

Overall, differences in diagnostic criteria and LC case definitions might account, at least in part, for both the variability in the proposed aetiopathogenic mechanisms and the inconsistencies in reported prevalence estimates and sex-related associations, underscoring the need for harmonised definitions and prospective studies.

Response to COVID-19 vaccine: role of sex and age

Vaccination and protection against severe COVID-19: COVID-19 vaccines play a crucial role in modulating the immune response to SARS-CoV-2 infection, helping to prevent immune dysregulation and reduce the risk of severe disease. Indeed, full vaccination and booster doses substantially reduce, though do not completely eliminate, the risk of severe COVID-19 outcomes [83]. The authors of the quoted study conducted a population-based cohort analysis across the four UK nations, using linked primary care, vaccination, hospitalisation, and mortality records. The analysis included individuals who received an autumn 2022 booster dose of either BNT162b2 or mRNA-1273 between September 1 and December 31, 2022, with the aim of evaluating the risk of severe COVID-19 outcomes. The models were adjusted for age,

sex, body mass index, socioeconomic deprivation, urban versus rural residence, and comorbidities. Analyses were stratified according to vaccine type, and pooled estimates across the four UK nations were obtained using fixed-effect meta-analysis. During the study period, a total of 7,451,890 individuals aged ≥ 18 years received an autumn booster dose. Severe COVID-19 outcomes were observed in 3,500 individuals, corresponding to 2.9 events per 1,000 person-years. Overall, males, older adults, underweight individuals, those with multiple comorbidities, residents of large households or deprived areas, and patients with specific chronic diseases remained at elevated risk of COVID-19 hospitalisation and mortality following the booster vaccination. These findings highlight that, despite the strong protective effect of vaccination, continued preventive measures and targeted therapies remain important, particularly for vulnerable populations [83].

To gain a deeper understanding of how the immune system responds to SARS-CoV-2 infection following vaccination, Chan et al. [84] conducted a comprehensive analysis of immune cells from both vaccinated and unvaccinated individuals who experienced mild to moderate COVID-19. At this stage, post-pandemic, it is important to note that the majority of SARS-CoV-2 infections occur in previously vaccinated individuals. To investigate immune responses in this context, the authors performed single-cell transcriptomic, proteomic, and functional profiling of both primary and post-vaccination infections, focusing on individuals affected during the Delta variant wave. Their findings revealed that individuals with post-vaccination infections exhibited less pronounced activation of transcriptomic signatures in monocytes and NK cells. This was accompanied by the upregulation of regulatory pathways that restrict monocyte trafficking and NK cell expansion. This modulation of innate immune activity might prevent excessive inflammation and tissue damage. However, the study also uncovered notable sex-specific differences. In females, innate immune cells exhibited greater transcriptomic and proteomic activation during breakthrough infections compared to males. Overall, these findings highlight that prior SARS-CoV-2 vaccination not only modulates the immune response during breakthrough infections but also prevents the overactivation of innate immunity, with clearly distinguishable sex-related patterns. These insights further underscore the broader potential of vaccination in mitigating immunopathological outcomes associated with hyperinflammatory responses [84].

Vaccination represents one of the most effective public health strategies, preventing millions of infections and deaths worldwide each year. Nevertheless, growing evidence indicates that vaccine-induced protection is not uniform across all populations. Variability in immune responses is influenced by multiple determinants, including genetic background, environmental exposures, such as microbiota, nutritional status, sex, and gender. Together, these determinants play a critical role in shaping individual responses to vaccination [85–87].

Determinants of vaccine responsiveness: In recent years, increasing attention has been directed toward the role of sex as a determinant of vaccine-induced immune responses. Evidence consistently shows that females tend to generate stronger antibody responses to vaccination and report adverse events more frequently than males. This greater immune reactivity in females is generally considered to contribute to their higher resistance to many infectious diseases [8, 53, 85–87]. However, findings related to COVID-19 vaccination remain inconsistent. Although a substantial body of work has examined immune responses to COVID-19 vaccines, sex as a biological variable has frequently been overlooked. In a systematic review, Sulis et al. [88] examined the extent to which studies on COVID-19 vaccine effectiveness reported sex-disaggregated data. Of the 240 publications reviewed, only 21 studies (8.8%) provided results stratified by sex, highlighting a significant gap in the current literature. Accordingly, the present analysis focuses on the most recent reviews, systematic reviews, and meta-analyses, with particular emphasis on age and sex-related differences in vaccine responsiveness.

Vaccination and LC: We begin by addressing the relationship between vaccination and LC, a condition in which, as previously discussed, differential immune responses may play a critical role. Vaccination against COVID-19 may reduce the risk of LC, although the magnitude of this protective effect remains uncertain. A systematic review [89] aimed to assess the vaccine efficacy/effectiveness of COVID-19 vaccines administered prior to SARS-CoV-2 infection in preventing LC. Efficacy reflects performance under ideal,

controlled clinical trial conditions, while effectiveness describes how a vaccine performs in real-world settings, across diverse populations and conditions [90]. In that systematic review, both randomised controlled trials and non-randomised studies of interventions (NRSI) evaluating pre-infection vaccination were considered eligible, regardless of participants' age or sex. From a total of 6,423 records screened, 65 NRSI reporting adjusted estimates were included, encompassing more than 5.7 million individuals. Overall, COVID-19 vaccination appears to confer moderate protection against LC, with some evidence suggesting that effectiveness may increase with a higher number of administered doses. However, the interpretability of subgroup analyses, such as those stratified by age, sex, and SARS-CoV-2 variant, was limited due to incomplete reporting in the available studies [89].

Dissociation between immunogenicity and clinical effectiveness: An important theme emerging from recent studies, as discussed below, is the apparent dissociation between vaccine immunogenicity and vaccine effectiveness. Females consistently develop stronger humoral immune responses following COVID-19 vaccination and report vaccine-related adverse events more frequently than males. However, this enhanced immunogenicity does not necessarily translate into greater real-world vaccine effectiveness, which appears comparable between the sexes and, in some studies, even relatively greater in males. This apparent paradox highlights that clinical protection depends not only on the magnitude of antibody responses but also on a complex interplay of factors, including baseline risk, age, immune regulation, and, possibly, exposomic influences.

Effects of age and sex on immunogenicity: The review of Fernandes et al. [91] examined antibody responses across different COVID-19 vaccine platforms, with particular attention to the influence of age and sex. Overall, several studies reported higher seropositivity rates and antibody levels in females compared to males following vaccination. For example, Bayram et al. [92] and Fonseca et al. [93] observed greater seropositivity in females after the first dose of the inactivated SARS-CoV-2 vaccine, with a clear age-related decline; younger individuals consistently showed higher response rates than older groups. Similarly, Li et al. [94] reported higher concentrations of spike-specific IgG and neutralising antibodies in females receiving inactivated vaccines, although no clear age effect was detected shortly after vaccination. In contrast, Choudhary et al. [95] found no statistically significant difference in antibody responses between individuals vaccinated with the inactivated SARS-CoV-2 vaccine and those vaccinated with the ChAdOx1nCoV-19 (AZD1222) recombinant viral vector vaccine. Evidence from mRNA vaccines also suggests an age-dependent decline in humoral responses. Khoury et al. [96] and Lustig et al. [97] reported lower antibody titres in older individuals vaccinated with BNT162b2, whereas younger participants exhibited significantly higher IgG levels. Notably, Khoury et al. [96] also found that older females had higher antibody responses than older males. Brisotto et al. [98] observed a negative correlation with age but no significant sex differences, while Kim et al. [99] reported no sex differences, with a faster decline in antibody levels among older subjects over time. In contrast, Fujigaki et al. [100] reported significantly higher IgG titres in females after the second dose of BNT162b2.

Findings from viral vector vaccines further highlight the combined influence of age and sex. Mishra et al. [101] reported a greater increase in antibody titres in females between the first and second doses of AZD1222, although antibody waning over time appeared more pronounced in females. Younger individuals (< 45 years) consistently exhibited higher antibody levels across all time points. Hernández-Bello et al. [102] also identified an inverse relationship between age and neutralizing antibody responses following Ad5.nCoV (another recombinant vaccine delivered by a viral vector) vaccination. Choudhary et al. [95] observed instead a trend (not significant) towards a difference between the sexes in recombinant viral vector vaccine (adenovirus-based; AZD1222) and inactivated whole-virion vaccine vaccinated cohorts.

Bachmann et al. [103] conducted a systematic review to evaluate the influence of age and sex on the efficacy and tolerability of mRNA vaccines against SARS-CoV-2. The review included English-language studies reporting post-vaccination neutralising antibody measurement, with some studies also reporting T-cell responses. After applying the inclusion criteria, 15 studies encompassing over 1.4 million participants were included [100, 104–117]. Across these studies, younger individuals consistently exhibited stronger humoral responses, with higher IgG and anti-spike antibody levels compared with older populations,

highlighting the impact of age on vaccine-induced immunity [100, 104–112]. Sex-related differences were also observed; females generally showed higher antibody titres and more robust immune responses than males, particularly among younger females [100, 105, 107, 109, 110, 112–114]. However, females also reported frequent adverse events, most commonly injection-site pain, fatigue, and headache, and a faster decline in antibody levels over time. Despite these differences, the overall severity of adverse reactions did not vary substantially across age or sex groups. Booster doses were effective in enhancing and sustaining antibody responses, particularly among older individuals, partially mitigating age-related immune declines in immunity [100, 106, 108, 110, 114]. Overall, these findings indicate that mRNA vaccines elicit strong immune responses, with age emerging as a key determinant and sex contributing to variability in both immunogenicity and reactogenicity [100, 109–111, 115]. However, Bignucolo et al. [118], in a systematic review and meta-analysis of clinical trials, reported higher vaccine efficacy in males than in females based on the incidence of new COVID-19 cases among vaccinated groups, while no sex differences were observed in control groups. In addition, pharmacovigilance data indicated a higher frequency of adverse events in females.

Sex-associated differences in vaccine effectiveness: Although females generally develop stronger humoral responses to vaccination, these immunological differences do not translate into greater vaccine effectiveness in real-world clinical settings. A nationwide retrospective cohort study conducted in Italy [119], linking vaccination registry data with national surveillance systems, further demonstrated that vaccine effectiveness was highest within 120 days post-vaccination across all age groups. Protection against severe disease was comparable between males and females, although males appeared somewhat better protected against infection. Zhu et al. [120] found no statistically significant sex differences in vaccine effectiveness, although a slight advantage was observed in males. These findings show that sex-related immunological differences do not necessarily correspond to differences in clinical practice, and the same goes for age and lower efficacy vs. equally good effectiveness [120].

Interpretation of the apparent paradox: Taken together, these studies suggest a general inverse association between age and vaccine-induced immune responses. While findings are not entirely uniform, most evidence suggests that females tend to mount stronger humoral responses to COVID-19 vaccines than males. However, the impact on real-world clinical effectiveness of sex-related differences in immune responses remains modest and context-dependent. Additional large-scale and stratified studies are needed to better define how sex interacts with age, vaccine type, and other determinants in shaping protective outcomes.

Thus, sex differences in COVID-19 vaccine effectiveness represent a complex and, at times, apparently paradoxical phenomenon. The discrepancy can be explained by differences between immunogenicity and clinical effectiveness. Males, who are at higher baseline risk of severe COVID-19 outcomes due to a combination of biological vulnerability and comorbidity burden, may experience a greater relative reduction in risk following vaccination, thereby giving the impression of higher vaccine effectiveness. In contrast, females often achieve a higher baseline level of immune activation, potentially approaching a threshold beyond which additional immune responses do not translate into proportionally greater clinical protection. These sex-related differences are rooted in multiple biological mechanisms, as discussed in the present review. In addition, ageing and immunosenescence further modulate these effects. Males tend to exhibit a more pronounced decline in biomarkers of immune function and a higher degree of inflamm-ageing, which may render them more responsive to the relative benefits of vaccination. Beyond intrinsic biology, exposome-related factors, including lifestyle, environmental exposures, comorbidities, and the gut microbiota, also shape susceptibility to infection and vaccine responsiveness in a sex-specific manner. Differences in occupational exposure, health behaviours, and social determinants of health may further influence infection risk and clinical outcomes, thereby indirectly affecting estimates of vaccine effectiveness.

Methodological limitations: Methodological limitations must also be considered, as many studies used heterogeneous endpoints such as infection, hospitalisation, or mortality. Together, these factors suggest that the observed higher effectiveness in males does not necessarily reflect superior vaccine-induced

immunity, but rather the interplay of baseline risk, immune regulation, ageing, and gendered-exposomic influences. Additional support for this interpretation comes from the observation that the most common adverse reactions to vaccination are more frequently reported in women than in men, as expected.

Conclusions: Females generally show stronger immunogenicity and greater reactogenicity. This does not translate into superior vaccine effectiveness. Real-world protection results from the interaction among immune responses, baseline risk, age, sex, gender-related factors, comorbidities, and the exposome.

Response to COVID-19 vaccine: vaccine-related adverse events

Females generally report vaccine-related adverse events more frequently than males and often express greater concerns about vaccine safety and effectiveness. Although most vaccine reactions are mild to moderate and broadly similar between sexes, several studies consistently show that females report higher rates of both local reactions (e.g., pain, redness, and swelling at the injection site) and systemic symptoms (e.g., fever, myalgia, headache, and hypersensitivity) following a variety of adult vaccines [121]. Adverse events associated with COVID-19 mRNA vaccines range from mild reactions, such as injection-site pain, to rare but severe outcomes, including anaphylaxis. However, age- and sex-specific patterns of these adverse effects remain incompletely characterised. To address this, Green et al. [122] analysed age- and sex-stratified data on adverse events following two or three doses of the BNT162b2 vaccine using four cross-sectional studies. Across all studies, adverse events were consistently reported more often by females than males across age groups and were particularly frequent after the second dose. These reactions included both local symptoms, such as injection-site pain, and systemic manifestations, including fever, fatigue, and myalgia. Female-to-male risk ratios ranged from approximately 1.8–1.9 in population surveys and exceeded 3.0 for several symptoms in workplace cohorts [121, 122].

The mechanisms underlying these sex-related differences remain uncertain. Possibly, biological differences in inflammatory responses to vaccination may contribute. Supporting this interpretation, studies examining objective indicators of inflammation, such as erythema and induration at the injection site after influenza vaccination, have shown that females can develop larger local reactions than males, suggesting that biological factors may play a role [121]. Another possibility is a gender-related reporting bias, whereby women may be more likely to report symptoms.

At the cellular level, sex differences in vaccine reactogenicity may partly reflect variations in mast cell and/or monocyte biology. Females appear more susceptible to mast cell-related conditions, including anaphylaxis, whereas perinatal androgen exposure in males may promote a mast cell phenotype with lower granule mediator content and reduced mediator release during degranulation, potentially limiting the severity of mast cell-mediated reactions. In addition, clinical and experimental studies indicate that females often experience more persistent inflammatory pain than males, possibly reflecting sex-specific immune mechanisms involved in pain resolution. Data from both animal models and human studies suggest that androgen-driven expansion of IL-10-producing monocytes promotes faster pain recovery in males through signalling via IL-10 receptors on sensory neurons, highlighting an immune pathway that may protect against the development of chronic pain [123, 124]. Overall, the consistent excess of adverse events reported among females following mRNA COVID-19 vaccination underscores the importance of systematically reporting vaccine safety data by sex. Consideration of sex-specific differences may also be relevant when evaluating vaccination strategies and could support future investigations into sex-tailored dosing approaches.

In contrast, the pattern of more severe adverse events, such as myocarditis and pericarditis, appears different. A recent systematic review and meta-analysis [125] assessed risks associated with COVID-19 vaccines, stratified by age, sex, vaccine type, and dose, and included 17 studies after screening. Compared with unvaccinated individuals or unvaccinated time periods, the highest attributable risk was observed after the second dose, particularly among boys aged 12–17 years receiving the BNT162b2 vaccine and young males aged 18–24 years receiving the mRNA-1273 vaccine. Stratified estimates from active surveillance data currently provide the most reliable evidence on population-specific risks. Importantly,

although relative risks may appear elevated in these subgroups, the absolute risk remains low. Moreover, accumulating evidence indicates that the risk of myocarditis is higher following SARS-CoV-2 infection than after vaccination, supporting the overall favourable risk–benefit profile of COVID-19 vaccines [126].

Response to COVID-19 vaccine: role of gender and exposome

Gender disparities span the entire vaccine continuum, from research and development to delivery and uptake. In vaccinology, sex and gender shape both biological responses and behavioural interactions with vaccines. Sex-based differences contribute to variability in immune responses, with females generally exhibiting greater reactogenicity than males, a feature that may also influence vaccine perceptions. These patterns are further modulated by exposomic factors, including environmental exposures, lifestyle, nutrition, and the gut microbiota, which collectively affect immune function and contribute to inter-individual variability in vaccine responsiveness. Concerns about adverse events are closely linked to vaccine hesitancy, with women more frequently reporting both side effects and their impact on daily activities, including sleep and caregiving. However, higher hesitancy does not necessarily translate into lower acceptance, although uptake remains uneven across populations. Reduced coverage among some ethnic minority women likely reflects disparities in healthcare access, socioeconomic conditions, institutional trust, and cultural norms. In certain settings, limited autonomy and reliance on family or community decision-makers may further constrain women's access to vaccination. Practical barriers, such as inconvenient service hours, geographic inaccessibility, and discriminatory healthcare experiences, also contribute to lower uptake, particularly among women and gender-diverse groups. These dynamics vary across HICs and LMICs, underscoring the importance of contextual and exposomic determinants. Additional concerns relate to the potential effects of vaccination on fertility and pregnancy, with vaccine uptake during pregnancy remaining lower than in the general population. This gap is partly reinforced by the historical exclusion of pregnant and breastfeeding women from clinical trials, despite their often elevated risk of infectious diseases. More broadly, structural and sociocultural constraints, including limited autonomy, financial barriers, and restricted health literacy, continue to hinder equitable access to vaccination. In contrast, settings characterised by greater gender equality tend to achieve higher vaccine coverage. Together, these observations highlight the need for sex- and gender-sensitive vaccination strategies that integrate biological, social, and exposomic perspectives, recognising that male and female exposomes may differ substantially, particularly in LMICs, and thereby influence both vaccine confidence and effectiveness [125–127].

Turning to vaccine hesitancy toward SARS-CoV-2 vaccines, a recent review highlights that it remains a significant issue in LMICs, particularly in East Africa, where approximately 40% of individuals report some degree of hesitancy. Alie et al. [128] identified several key determinants, including female sex, younger age (under 40 years), inadequate preventive practices, and reliance on internet-based information sources. Additional contributing factors include negative attitudes toward vaccination, concerns about vaccine safety, fear of adverse effects, uncertainty regarding the risk of COVID-19 infection, and endorsement of conspiracy beliefs. Importantly, many of these factors are inherently gender-related, reinforcing the notion that gender is a key driver of vaccine hesitancy in this context [129]. However, a recent study conducted in southern Italy investigating barriers to COVID-19 booster vaccination found no overall sex differences in hesitancy. Nevertheless, the steepest decline in booster uptake was observed among younger and middle-aged adults, particularly men living in highly socioeconomically deprived areas [130].

Recent findings suggest a modulatory role of the gut microbiota in shaping the immune response [65, 70], including that to the mRNA-1273 SARS-CoV-2 vaccine, thus, microbial metabolic functions might represent potential targets for enhancing vaccine efficacy within personalised immunisation strategies. In this context, a study analysed gut microbiota and anti-spike IgG in 50 healthcare workers who received the mRNA-1273 vaccine. Participants were stratified into low, medium, and high responders based on IgG titres measured 30 days after vaccination, and baseline faecal samples were collected for microbiome analysis. A higher relative abundance of Clostridia, Clostridiales, Ruminococcaceae, and *Odoribacter splanchnicus* was associated with stronger IgG responses. Functional microbiome analysis further revealed an enrichment of

acetate-producing metabolic pathways in high responders, suggesting a potential role of short-chain fatty acids (SCFAs) in enhancing vaccine-induced immunity. Conversely, taxa such as *Hallella* and *Sutterella wadsworthensis* were associated with weaker immune responses [64]. More broadly, microbial-derived metabolites, particularly SCFAs such as butyrate, acetate, and propionate, along with microbial-associated molecular patterns, including lipopolysaccharide, flagellin, and peptidoglycan, act as key modulators of vaccine immunogenicity and efficacy. These components might function as natural adjuvants, strengthening both innate and adaptive immune responses. However, as previously discussed, the picture is further complicated by the influence of other gender-related factors, such as diet, lifestyle, and behavioural patterns, on microbiota composition [66–69].

In the post-Omicron era, immune protection is increasingly shaped by hybrid immunity, resulting from the combination of vaccination and natural infection. Whether sex, gender, and exposome influence the magnitude, durability, and clinical consequences of hybrid immunity remains incompletely understood and warrants further investigation [131].

Sex and determinants of immune responses to SARS-CoV-2 vaccination are depicted in Figure 2.

FEMALES	MALES
↑ Monocyte trafficking	↓ Biomarkers of immune function
↑ NK cell activation	↑ Inflamm-ageing
↑ Antibody response but with a faster decline in antibody levels over time	Faster pain recovery because of androgen-driven expansion of IL-10–producing monocytes
↑ Side effects injection-site pain, fatigue, and headache, susceptible to mast cell–related conditions	Fewer but sometimes different types of adverse events according to age stratification (*e.g.*, myocarditis)

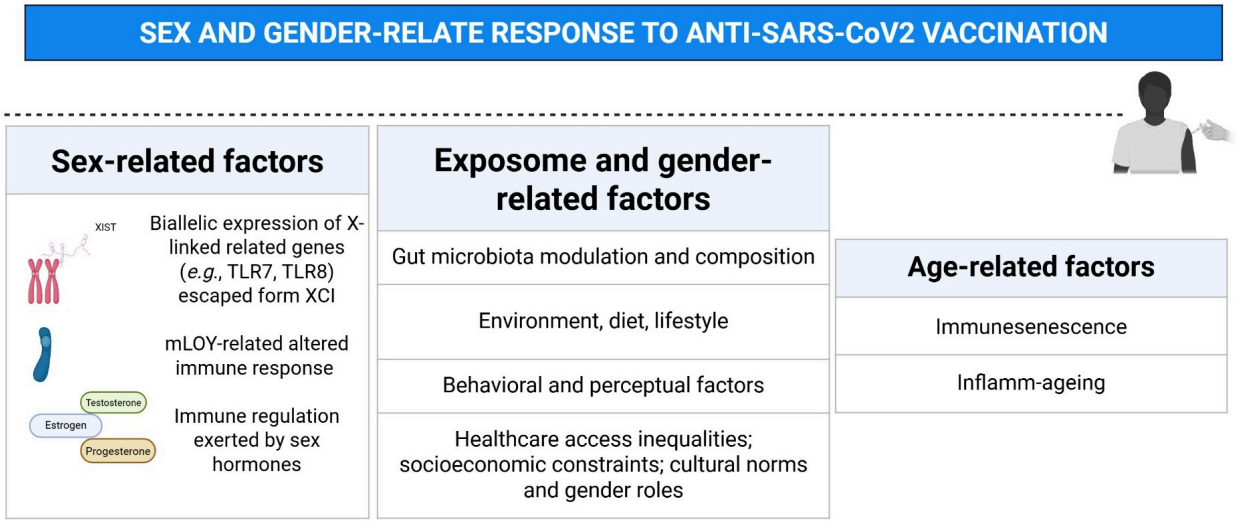

Figure 2. Sex- and gender-related differences in immune responses to SARS-CoV-2 vaccination. Overview of biological (sex), environmental (exposome), gender, and age-related factors shaping vaccine-induced immunity. Females generally exhibit stronger innate and adaptive immune responses, including enhanced monocyte trafficking, NK cell activation, and higher antibody production, but also a higher frequency of reactogenicity and mast cell-related adverse events. Males display lower immune activation, features of inflamm-ageing, and reduced reactogenicity, although certain age-dependent adverse events (e.g., myocarditis) may occur. These differences are influenced by X-linked gene expression escaping X-chromosome inactivation, sex hormone-mediated immune modulation, mLOY-associated alterations, as well as microbiota composition, lifestyle, socioeconomic factors, and immunosenescence. For references, see text. Created in BioRender. Calabrò, A. (2026) https://BioRender.com/fsgdis8.

Conclusions

Disparities in responses to COVID-19 infection cannot be explained solely by biological sex-related factors. Rather, they arise from the interplay of sex, age, gendered social roles, and exposomic influences, including

occupational exposures, environmental factors, the microbiota, health-related behaviours, and structural inequalities linked to socioeconomic conditions. Analyses that disaggregate data by sex reveal substantial heterogeneity in outcomes, heterogeneity that is often obscured in studies that merely adjust for sex without exploring its interaction with other determinants. Notably, societies characterised by greater gender inequality tend to exhibit wider mortality gaps between women and men, underscoring the central role of social and structural contexts. While biological sex remains an important determinant, it must be examined within this broader framework of social and environmental interactions. This perspective aligns with emerging research emphasising the interconnected nature of sex and gender, moving beyond rigid dichotomies toward an integrated understanding of biology as shaped by social and ecological contexts [128].

Importantly, these patterns are not unique to COVID-19 but are observed across a wide range of health conditions, reflecting the pervasive influence of structural and contextual inequities. This underscores the need to systematically incorporate gender-sensitive and intersectional approaches into biomedical research, public health strategies, and healthcare policy. Within this framework, sex and gender are also key determinants of vaccine responses.

One of the key messages emerging from this review is that stronger vaccine-induced immune responses do not necessarily translate into greater clinical protection. The apparent paradox whereby females develop more robust humoral responses while vaccine effectiveness remains broadly comparable between the sexes, or even relatively greater in males, underscores the importance of distinguishing immunogenicity from clinical effectiveness. Both should be interpreted within the broader context of interacting biological and environmental determinants, including sex, gender, age, and the exposome (Figure 3). Consistent with this interpretation, women report adverse reactions more frequently than men. However, the interpretation of many sex- and gender-related differences should take into account the dynamic nature of the pandemic. The emergence of successive SARS-CoV-2 variants, together with the widespread development of hybrid immunity and continuous improvements in clinical management, has progressively reshaped disease severity, the burden of LC, and the real-world effectiveness of COVID-19 vaccines. These evolving factors should be considered when interpreting sex- and gender-specific findings across different phases of the pandemic.

Lessons learned from the COVID-19 pandemic, together with persistent challenges in vaccine acceptance, highlight the importance of transparent communication, recognition of sex- and gender-related differences, and the integration of biological, behavioural, and exposomic perspectives to optimise vaccination strategies. Incorporating sex and gender into vaccine development, policy, and implementation is therefore essential for advancing precision vaccinology. Although vaccines have traditionally been designed to provide uniform protection, a more tailored approach that accounts for both biological and social determinants of immune responses is increasingly necessary to improve public health outcomes.

Future perspectives

Future research should move beyond considering sex and gender as simple covariates and instead recognise them as interacting biological and social determinants operating throughout the entire life course. Combining sex chromosome complement, hormonal status, ageing, the exposome, the microbiota, and multi-omics approaches with longitudinal clinical studies will provide deeper insights into the mechanisms underlying interindividual variability in susceptibility to infection, disease severity, LC, and vaccine responsiveness. Artificial intelligence and systems biology are expected to facilitate the integration of these multidimensional datasets, paving the way for enabling the development of predictive models capable of supporting personalised prevention, vaccination and treatment strategies. In addition, exceptionally long-lived individuals may represent a unique human model for identifying protective immune mechanisms that promote resilience to emerging infectious diseases and healthy immune ageing.

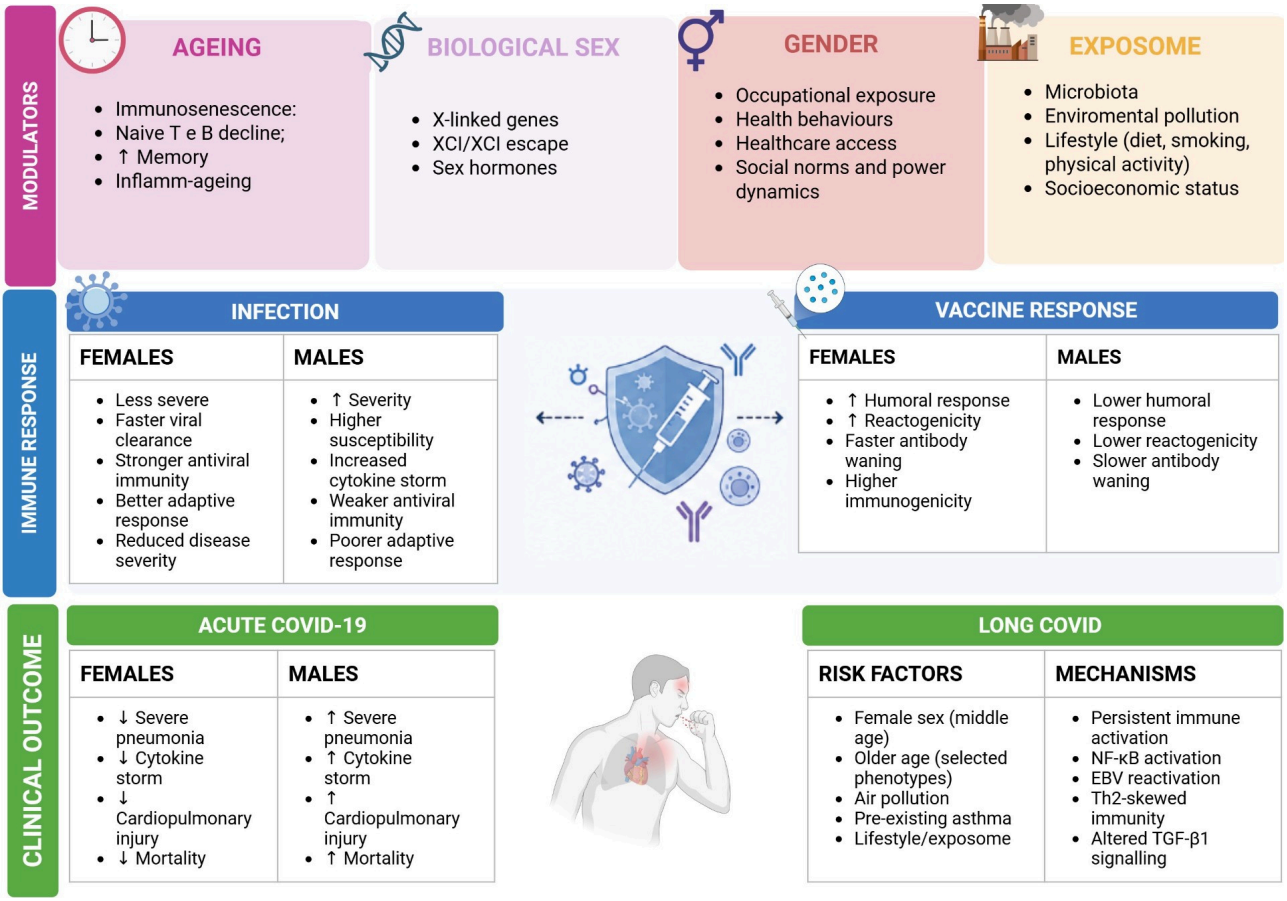

Figure 3. Interplay of ageing, biological sex, gender, and the exposome in shaping immune responses and clinical outcomes of SARS-CoV-2 infection and vaccination. Ageing, sex-related biological factors, gender-related determinants, and exposome-associated influences act as interconnected modulators of immune function. Their combined effects contribute to differences between females and males in antiviral responses, viral clearance, inflammatory activation, disease severity, and mortality during acute COVID-19, as well as in humoral responses, reactogenicity, immunogenicity, and antibody waning after vaccination. Long COVID is influenced by both sex-associated and environmental or clinical risk factors. It may involve persistent immune activation, autoimmunity, Epstein-Barr virus reactivation, T helper 2-skewed responses, and altered TGF-β1 signalling. The relationships shown are simplified and should not be interpreted as deterministic, as substantial heterogeneity exists within both females and males. Created in BioRender. Calabrò, A. (2026) https://BioRender.com/4ydlv06.

Abbreviations

ACE: angiotensin-converting enzyme

COVID-19: coronavirus-19 disease

DCs: dendritic cells

EBV: Epstein-Barr Virus

ETS1: E26 transformation-specific 1

HICs: high-income countries

ICU: intensive care unit

IFN-I: type I interferon

IgG: immunoglobulin G

LC: Long COVID

LMIC: low- and middle-income countries

mLOY: mosaic loss of the Y chromosome

NK: natural killer

NRSI: non-randomised studies of interventions

PM: particulate matter

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SCFAs: short-chain fatty acids

TGF-β: transforming growth factor-β

Th1: T helper 1

TLR: toll-like receptor

TMPRSS2: transmembrane serine protease 2

TSPO: translocator protein

WHO: World Health Organisation

XCI: X-chromosome inactivation

Declarations

Author contributions

CMT: Conceptualisation, Investigation, Writing—original draft, Writing—review & editing. GA: Writing—review & editing. AC: Investigation, Writing—original draft, Writing—review & editing. EM: Writing—review & editing. GP: Writing—review & editing. CC: Conceptualisation, Investigation, Writing—original draft, Writing—review & editing, Supervision. All authors read and approved the submitted version.

Conflicts of interest

Emanuele Montomoli is the founder and Chief Scientific Officer of VisMederi srl. Calogero Caruso, who is the Editor-in-Chief of *Exploration of Immunology*, had no involvement in the decision-making or the review process of this manuscript. The other authors declare no conflicts of interest.

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