# **PERSPECTIVES**

**Are sex disparities in COVID-19 a predictable outcome of failing men’s health provision?**

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**Abstract |** The COVID-19 pandemic, caused by the SARS-CoV2 coronavirus, has taken a catastrophic toll on society, health-care systems and the economy. Notably, COVID-19 has been shown to be associated with a higher mortality rate in men than women. This disparity is likely to be a consequence of a failure to invest in men’s health, as it has also been established that men have a lower life expectancy and poorer outcomes from non-communicable diseases than women. A variety of biological, social and economic factors have contributed to the sex disparities in mortality from COVID-19. A streamlined men’s health programme — with the urologist as the gatekeeper of men’s health — is needed to help prevent future tragedies of this nature.

[H1]**Introduction**

In December 2019, a novel coronavirus (subsequently termed SARS-CoV-2) was first reported in China; the resulting disease was coined COVID-19(1). This virus has subsequently spread globally, causing a pandemic that has had a catastrophic effect on society, health-care systems and the economy. Considerable media and public interest has focussed on the disproportionately high mortality from COVID-19 in men(2); his discrepancy might due to biological, genetic and lifestyle differences between the sexes, making men more vulnerable to both infections and non-communicable diseases(3–5). Indeed, this sex gap in mortality is not a new phenomenon and contemporary health-care policies seem to have failed to adequately address the disproportionately high levels of premature male deaths(3).

In this Perspective, we will highlight the potential factors contributing to sex discrepancies in mortality from COVID-19, provide a rationale for the development of a men’s health programme and discusses the role of the urologist in this setting.

**[H1]What is COVID-19?**

SARS-CoV-2is a subgenus Sarbecovirus of the genus Betacoronavirus(1). The pathogenesis of COVID-19 is still poorly understood, but it has been speculated that the SARS-CoV-2 first binds to the Angiotensin-converting enzyme 2 receptor (ACE2) on the surface of epithelial cells in the nasal cavity(6)(7), after which it propagates and spreads across the respiratory tract causing an innate immune response with cytokine secretion and an inflammatory response(8). This immune response results in an influx of pulmonary infiltrates, apoptosis of alveolar type II cells and diffuse alveolar damage, leading to subsequent fibrosis, acute respiratory distress syndrome (ARDS) and microvascular thrombi(7)(9)(10).

The first cases of COVID-19 were reported in December 2019; by the end of February 2020, 55,924 cases had been confirmed(11). The infection has now spread globally with over 234 million confirmed cases (43 million in the US alone) and 4.7 million deaths as of October 2021(12)

A sex-disaggregated data tracker has highlighted a gender difference worldwide(13). Although cases of COVID-19 have an almost equal division between men and women, more men are hospitalised, admitted to intensive care, and die from infection (Figure 1).

**[H1]Risk factors for mortality and sex**

The first confirmed human cases of COVID-19 were reported in China’s Hubei province(14). Several studies of patients from this region describe prognostic factors for survival after COVID-19 infection. A study of a cohort of 191 patients from two hospitals within Wuhan(15) reported that the clinical factors associated with COVID-19 mortality were increasing age (69 years (Interquartile range (IQR):63–76) versus 52 years (IQR:45–58) p<0.0001), hypertension (p= 0.0008), diabetes (p=0.0051), cardiovascular disease (CVD) (p<0.0001), chronic obstructive lung disease (COPD) (p=0.047) and chronic kidney disease (p=0.024)(15). Moreover, multivariable regression analysis confirmed that older age was associated with increased mortality (odds ratio (OR): 1.10, 95% Confidence Interval (CI): 1.03–1.17, per year increase, p=0.0043). A prospective cohort study of 179 patients with COVID-19 who were hospitalised at Wuhan Pulmonary Hospital, reported that patients who died were much older than those in the survivor group (mean age +/- standard difference; 70.2±7.7 years versus 56.0±13.5 years, p<0.001)) and had hypertension (61.9% versus 28.5%, p=0.005) and CVD or cerebrovascular diseases (57.1% versus 10.8%; p<0.001)(16). Multivariate analysis showed that an age ≥65 years (OR: 3.765, 95% CI:1.146‒17.394, p=0.023) and cardiovascular or cerebrovascular comorbidities (OR: 2.464, 95% CI: 0.755‒8.044, p=0.007) were associated with an increased risk of COVID-19 mortality. Accordingly, a retrospective case series of 201 patients who were admitted to a single hospital in Wuhan with COVID-19 showed that patients who developed ARDS were older (median age 58.5 (IQR 50-69) versus 48 (IQR:40-54), p< 0.001) and had a history of hypertension (23% versus 16%, p=0.02) and diabetes (16% versus 6%, p=0.002) than those who did not develop ARDS. These conclusions were also supported by a study investigating the clinical factors associated with COVID-19 disease severity and mortality in a cohort of 663 Chinese patients from a single hospital in Wuhan(17). In this study, disease severity was classified according the WHO guidelines for clinical management of COVID-19 (18)and patient age ≥60 years was associated with severe and critical disease severity compared with mild and moderate categories (p<0.001) and also increased mortality (p=0.004). The presence of pre-existing respiratory disease (p= 0.003), CVD (p <0.001) and endocrine diseases (p = 0.007) were independently associated with increased COVID-19 disease severity. However, only respiratory disease (p=0.019) and CVD (p<0.001) were also associated with increased COVID-19 mortality.

Studies examining COVID-19 in other areas of China have reported similar findings to those that have focussed on the Wuhan region. Wan et al.(19) studied the clinical presentation of 135 patients admitted to a single hospital in the Chongqing region. The authors assessed severity using the WHO guidelines(18) and reported that severe disease was associated with increased age (median age 56 years (IQR 52-73) versus 44 years for mild disease (IQR 33-49), p<0.001) and underlying comorbidities (70% versus 16.3%, p<0.0001). A meta-analysis that pooled data from 11 studies in China reported that COPD was significantly associated with mechanical ventilation, critical care admission or death from COVID-19 (OR: 6.44, 95% CI:1.85‐22.46) (20). In accordance with these data, a separate meta-analysis comprising 7 studies from China observed that smoking was associated with worsening severity of COVID-19 (OR: 2.16, 95% CI:1.45‐3.22)(21).

These studies suggest that increasing age, male sex and certain comorbidities — in particular hypertension, diabetes, CVD and COPD — are risk factors for COVID-19 mortality and worsening severity.

Data from other countries have reported similar findings. Giacomelli et al.(22) performed a single-centre, prospective cohort study of patients with COVID-19 admitted to the Luigi Sacco Hospital in Milan between 21st February 2020 and 19th March 2020. Mortality was associated with increasing age, with a higher proportion of deaths than survivors in the 66−75 years (39.6 % versus 19.5 %), 76−85 years (20.8 % versus 13.0 %), and 86−95 years (10.4 % versus 2.7 %) age groups (all p<0.001). Cardiovascular disease seemed to be associated with increased COVID-19 mortality, as a higher mortality rate was observed in those taking anti-platelet agents (p=0.009), calcium channel blockers (p=0.023) and angiotensin II receptor blockers (p=0.001). Univariate and multivariable Cox analysis showed that age (adjusted hazard ratio (HR): 2.08, 95 % CI 1.48−2.92 per ten years more) and obesity (adjusted HR: 3.04, 95 % CI 1.42−6.49) were independently associated with an increased risk of death.

A study that compared the clinical outcomes of COVID-19 between Italy and China using records from the National Italian Institute of health and the Chinese Centre for Disease Control and Prevention reported that The COVID-19 mortality rate was significantly higher in Italy than in China (OR: 3.18, 95% CI, 3.06-3.31, p<0.001)(23). Moreover, the presence of several comorbidities (Diabetes (OR: 1.82, 95% CI:1.22-2.15), Hypertension (OR: 3.46, 95% CI:2.68-4.46), Chronic respiratory disease (OR: 2.30, 95% CI:1.54-3.44), Cancer (OR: 11.73, 95% CI:5.14-28.77) and CVD (OR: 1.91, 95% CI:1.45-2.50) were associated with a higher risk of death in the Italian patients than in the Chinese population. The authors also reported that male sex (OR:1.27, 95% CI:1.11-1.46) and an age >60 (OR: 4.63, 95% CI:3.87-5.55) were associated with a higher risk of mortality in the Italian than the Chinese population and the presence of either of these factors conferred a two-fold higher risk of COVID-19 death in Italy than China (OR: 2.01, 95% CI:0.54-7.52, p=0.00).

The reason for this discrepancy in mortality rates between countries is uncertain but it might reflect population demographics and public health-care strategies. Several studies (15)(22)(23) have reported that increasing age is associated with a higher COVID-19 mortality and the average age of the Italian population is 46.7 years, which is 7 years older than that of China(24). A study comparing mortality rates by age group in China and Italy reported that 52.3% of the total deaths (n=850) in Italy occurred in those aged ≥80 years, whereas this age group only accounted for 20.3% (n=208) of deaths in China(25). These data suggest that Italy had a higher COVID-19 mortality rate than China because the Italian population was older than that of China and increasing age is a risk for COVID-19 death.

Differences in health-care systems and polices might have also contributed to the higher mortality rate in Italy compared with China. Italy had a much higher number of reported cases than China (219,070 versus 82,918 in the time period 31st December 2019 to 10th May 2020 (26), which might relate the higher number of deaths. Furthermore, in Italy, the high number of cases overwhelmed the health-care systems in the worse affected regions of the country, reducing the available resources for those patients who were unwell with COVID-19(24). The increased number of cases in Italy compared with China is likely to be a culmination of political and health-care policies. Soon after the outbreak of COVID-19, the Chinese government enforced a lockdown of the city of Wuhan and other cities in the Hubei province, employed a travel quarantine, postponed reopening of schools and set up temperature screening checkpoints(27). Moreover, the Chinese government mandated the use of face masks in public areas and set up two emergency hospitals that provided 2,400 beds(28). Moreover, outdoor restriction measures were put into place, whereby only one member of each household was permitted to go outside at scheduled times(28). By contrast, the mayor of Milan launched a campaign with the headline ‘Milan don’t stop’, which was designed to encourage social mobility(24). Although the first cases of COVID-19 were reported in Italy at the end of January, lockdown of affected areas only occurred at the end of February and schools weren’t closed until early March(24). Thus, despite having more time to prepare and the benefit of China’s experience with the virus, Italy was slow to mitigate the transmission of the virus.

Emerging data from New York have also suggested that age and comorbidities are associated with an increased risk of COVID-19 mortality. Mikami et al.(29) studied the clinical characteristics of 6,493 patients in  8 hospitals in New York City. They reported that COVID-19 hospital mortality was increased in the 50-74 years (HR: 2.34, 95% CI:1.47–3.71, p<0.001) and ≥75 years (HR: 4.85, 95% CI:2.75–8.56, p<0.001) age groups. Moreover, being female was associated with decreased hospital mortality (HR: 0.84, 95% CI 0.77–0.90). A separate study reported the clinical outcomes of COVID-19 at two New York hospitals(30). In this study, multivariable Cox analysis showed that older age (adjusted HR: 1·31, 95% CI:1·09–1·57, per 10-year increase), chronic cardiac disease (adjusted HR:1·76, 95% CI:1·08–2·86) and chronic pulmonary disease (adjusted HR 2·94, 95% CI:1·48–5·84) were independently associated with hospital mortality.

Within the UK, several large observational studies have investigated factors associated with COVID-19 mortality. The openSAFELY study (31) analysed the health records of 17,425,445 NHS patients of whom 5,683 died of COVID-19. COVID-19 mortality was associated with male sex (HR:1.99, 95% CI:1.88-2.10), increasing age ((ages 60-69: (HR: 2.09); 70-79 (HR: 4.77); ≥ 80 (HR: 12.64)), social deprivation (HR: 1.75, 95% CI: 1.60-1.91); uncontrolled diabetes (HR: 2.36, 95% CI: 2.18-2.56) and severe asthma (HR: 1.25, 95% CI: 1.08-1.44). A prospective observational cohort study in 208 acute hospitals in the UK s reported that increasing age was associated with COVID-19 mortality (50-59 years (HR: 2.63, p<0.001), 60-69 years (HR: 4.99, p<0.001), 70-79 years (HR: 8.51, p<0.001) and ≥80 years (HR:11.09, p<0.001)(32). Other factors reported to be associated with increased COVID-19 mortality were chronic cardiac disease (HR: 1.16, 95% CI:1.08-1.24, p<0.001), chronic non-asthmatic pulmonary disease (HR: 1.17, 95% CI:1.09-1.27, p<0.001), chronic kidney disease (HR: 1.28, 95% CI:1.18-1.39, p<0.001), obesity (HR: 1.33, 95% CI:1.19-1.49, p<0.001), chronic neurological disorder (HR: 1.17, 95% CI:1.06-1.29, p=0.001), dementia (HR: 1.40, 95% CI:1.28-1.52, p<0.001), malignancy (HR: 1.13, 95% CI:1.02-1.24, p=0.017), and liver disease (HR: 1.51, 95% CI:1.21-1.88, p<0.001). Female sex was associated with lower mortality (HR: 0.81, 95% CI 0.75 to 0.86, p<0.001). A population cohort study using data from England assessed whether the presence of diabetes affected the risk of COVID-19 mortality(33). The authors reported that the factors associated with increased COVID-19 mortality were male sex (OR: 1.94, 95% CI:1.89-1.99, p<0.001), increasing age (70-79 years OR: 2.64, 95% CI:2.53-2.76, p<0.001 and ≥80 years OR: 9.20, 95% CI:8.83-9.58, p<0.001), social deprivation (OR: 1.88, 95% CI:1.80-1.96, p<0.001), black ethnicity (OR: 1.71, 95% CI:1.61-1.82, p<0.001), Asian ethnicity (OR: 1.35, 95% CI:1.28-1.42, p<0.001), type 1 diabetes (OR:3.51, 95% CI:3∙16-3∙90, p<0.001) and type 2 diabetes (OR: 2.03, 95% CI:1.97-2.09, p<0.001).

Reflecting the data from China, these studies suggest that the main risk factors for COVID-19 mortality and severity are male sex, increasing age, cigarette smoking and certain comorbidities (hypertension, cardiovascular diseases, COPD and diabetes).

Within this context, that men have a higher mortality rate from COVID-19 is unsurprising, given that men have a higher incidence of cardiovascular disease, hypertension, type 2 diabetes, COPD, and tobacco use than women. A WHO report (34) observed that worldwide, the prevalence of smoking is higher for men than for women (40% versus 9%) and that men account for 80% of all smokers. This trend is consistent in all continents with a higher percentage of men than women being smokers in Africa (33.3% versus 8.2%), Asia (46.1% versus 9.6%), the Americas (37.9% versus 18.0%), Middle East (44.6% versus 9.0%), Eastern Europe (47.2% versus 20.9%) and Western Europe (30.1% versus 23.4%)(35). Cigarette smoking is an risk factor for COPD(36), CVD(37)(38) and several malignancies (lung, hepatic, oral cavity, bladder, oesophageal, pancreatic, gastric, renal, lymphoma cancers)(39). A 2018 meta-analysis of 156 studies on COPD data reported a higher prevalence of the disease in men than women (9.23% versus 6.16%)(40).

Thus, the higher prevalence of cigarette smoking and COPD in men than women might also predispose to worse COVID-19 outcomes.

The National England and Wales Diabetes Audit(41) reported a male predominance in both type 1 (57% vs 43%) and type 2 diabetes (58% versus 42%) diagnoses during 2019–2020.

The incidence of type 1 diabetes in childhood has been reported to disproportionately affect men compared with women (55% versus 45%)(42)(43) and a nationwide Swedish study reported a significantly higher male incidence of type 1 diabetes (20.5/100,000/year) compared with the incidence in females (12.7/100,000/year, p<0.001)(44). A nationwide Chinese study comprising 46,239 adults observed an age-standardised prevalence of type 2 diabetes at 10.6% among men and 8.8% among women (p<0.001)(45). Moreover, multivariable analysis showed that the male sex was associated with an increased risk of type 2 diabetes (OR 1.26 95% CI 1.12-1.43, p<0.001)(45).

A population study compared the overall rates of diabetes in Ontario, Canada during 1995–2005. The authors observed that incidence and prevalence of diabetes were higher in men than women (both p<0.0001) (46). Indeed, the worldwide age-standardised adult diabetes prevalence in men has been reported to be 9.0% compared with 7.9% in women(47).

Furthermore, evidence suggests that men are more susceptible to developing diabetes at a lower body mass index (BMI) than women. Analysis of a diabetes register in Scotland that included 51,920 men and 43,137 women showed that the mean BMI at diagnosis of diabetes was 31.83 kg/m2 in men and 33.69 kg/m2 in women (48). Moreover, the authors observed an inverse relationship between age and BMI at diagnosis of type 2 diabetes and the slope was steeper in women than in men (slope estimate for men was -0.12 kg/m2 per year compared with 0.18 kg/m2 per year in women, p<0.0001).

The cause of these sex discrepancies in diabetes have been speculated to be related to sex differences in insulin sensitivity and fat distribution. MRI-based comparison of visceral and subcutaneous adipose tissue in men and women demonstrated a significantly higher visceral adipose tissue volume (mean litres +/- standard deviation) in men than women in both white (3.40+/-2.12 versus 1.69 ± 1.24, p<0.05) and African-American (2.48+/- 1.66 vs 1.72 +/- 1.03, p<0.05) cohorts(49). Furthermore, females were noted to have a higher volume (mean litres+/- standard deviation) of subcutaneous adipose tissue than men in both the white (4.86 ± 2.0 vs 3.92 ± 2.11; p<0.05) and African American (6.58 ± 3.42 vs 3.92 ± 2.40; p<0.05) cohorts(49). These results have been supported by a separate study that also compared adipose tissue distribution in different sexes using MRI, which showed that women had a significantly higher volume (litres) of subcutaneous adipose tissue than men (39.6 +/- 11.6 versus 30.7 +/- 7.5, p<0.01)) but significantly lower volumes of visceral adipose tissue and lean tissue (2.5 +/- 1.1 versus 4.8 +/- 2.1 p<0.01 and 42.8 +/- 4.7 versus 58.2 +/- 6.2 L, respectively; p<0.01)(50). A study in which annual measurements of body composition and fat distribution were assessed in 153 women reported that, although increasing age was associated with increased subcutaneous fat (p<0.001), visceral fat only significantly increased in women who became post-menopausal (80.8 to 101.7cm2, p<0.05)(51). Animal data have demonstrated that visceral as opposed to subcutaneous, adipose tissue confers to metabolic changes that can increase susceptibility to diabetes. For example, in a mouse study, after transplantation of epididymal fat pads into either the parietal peritoneum (draining into the caval or systematic venous system) or mesenterium (the portal venous drainage system), mice with a fat transplant in the mesenterium had a significantly higher glucose concentration after an intraperitoneal glucose load than the mice that received a fat transplant in the peritoneum (p<0.001)(52). This glucose concentration corresponded with an increase in portal but not systematic IL-6 concentrations. Application of a hyperinsulinemic-euglycemic clamp to both sham-operated and fat-transplanted mice resulted in an insulin-induced suppression of endogenous glucose production in sham-operated mice, but this effect was blunted in mice with a mesenterium fat transplant (p<0.05). Collectively these data suggest that mice with fat pad transplants in the mesenterium developed hepatic insulin resistance and impaired glucose tolerance, which was associated with an increase in cytokine Il-6. Thus, men might develop diabetes at a lower BMI than women because they have a higher proportion of visceral adipose tissue, which might increase their insulin resistance.

Although not specific to sex, male obesity rates are rising and the average BMI has increased by 3.3kg/m2 within a 39 year period (1975–2014)(53)(3). This increase is especially relevant as one European study highlighted that obesity was associated with an increased use of mechanical ventilation following COVID-19 infection(54). Simonet et al. investigated the association between BMI and the requirement for invasive mechanical ventilation in patients infected with COVID-19 admitted to the intensive care unit at the Roger Salengro Hospital between 27th February 2020 and 5th April 2020(54). The authors observed that the patients that required invasive mechanical ventilation had a significantly higher median BMI than those who did not (31.1kg/m2 versus 27 kg/m2, p<0.001).

A WHO study reported that, globally, the mean systolic blood pressure (age-standardized estimate) was 127.0 (125.7-128.3) in men compared with 122.3 (121.0-123.6) in women(55). In accordance with these data, a study using data from The National Health and Nutrition Examination Survey (NHANES) reported that, in the USA the prevalence of hypertension was higher in men than women in all age groups(56). However, this gap in hypertension prevalence between the sexes narrowed with age; in the 18-39-years group, the difference in prevalence rate between men and women was 18.2%, whereas in the >60 years group the difference reduced to just 1.3%. Tamara et al. investigated sex differences in age-related stiffening of large arteries in a cohort of 123 participants at a single institution(57). The authors observed that the brachial and carotid pulse pressures were significantly lower in young women (mean age 23 years) than in men of the same age (p**<**0.01) but significantly higher in women than men in the elderly population (mean age 62 years) (p**<**0.05). The same study also compared systemic arterial compliance (SAC) in both sexes and observed no sex difference in SAC in the young cohorts (mean age 23 years) but in the older group (mean age 62 years), women had a lower SAC than men (0.27 **+/-** 0.03 vs 0.57 **+/-** 0.04, p**<**0.001). The authors reported that FSH levels were significantly increased in the older group compared with the younger group and FSH correlated strongly with indices of central arterial function (r= 0.39-0.65). Thus, increasing age is associated with a more pronounced stiffening of large arteries in females than males and this discrepancy corresponds with changes in FSH.

Sex differences in hypertension prevalence might also be related to lifestyle factors. In addition to the higher prevalence of smoking in men than women, men also have a higher salt intake. In 2014, the national diet and nutrition survey in the UK reported that men had a mean daily salt intake of 9.1g/day, whereas women consumed an average 6.8g/day(58). Moreover, the mean sodium intake in the USA estimated using 24-hour urinary excretion was 4,205 mg/d in males and 3,039 mg/d in females(59).

The higher prevalence of hypertension, smoking and diabetes might also account for the higher levels of coronary heart disease reported in men than women. The WHO mortality database reported a fourfold higher coronary heart disease mortality rate in men than women aged 30-64 years and twofold in those aged 65-89 years(60). Furthermore, a study of NHANES data reported that the US prevalence of CVD in men was 61, 500, 000 (51.2% of the population) compared with 60, 000, 000 (44.7% of the population) in women(59). The UK Biobank was a large prospective study of 502,628 participants recruited between 2006 and 2010(61). The study reported that the incidence rates of myocardial infarction per 10 000 person years were 7.76 (95% CI: 7.37 to 8.16) in women and 24.35 (95% CI: 23.57 to 25.16) in men(61). Data also show that men develop CVD at an earlier age than women. In a prospective cohort study from the Netherlands that included 8,419 participants and studied the average age of the first manifestation of coronary heart disease(62), men between the ages 55-64 years had a significantly higher lifetime risk of the first manifestations of coronary heart disease than women (27.2 % versus 16.9%, p<0.001). In the INTERHEART global case-control study, which included 27,098 participants from 52 countries, the median age of the first acute myocardial infarction was higher in women than men (65 versus 56 years; p<0.0001)(63). This delay in CVD onset has been attributed to the cardioprotective effects of oestrogen in premenopausal women. Several studies have shown that bilateral oophorectomy confers a higher risk of CVD compared to an age-matched control group of women who have not undergone the procedure (64)(65). Rivera et al.(64) reported that women who underwent bilateral oophorectomy before the age of 45 years had an increased mortality associated with CVD compared with age-matched controls (HR: 1.44, 95% CI:1.01–2.05, p*=*0.04). Furthermore, those treated with oestrogen replacement therapy following surgery and up to the age of 45 years or longer had no significant increase in mortality compared with a control cohort (HR: 0.65, 95% CI:0.30–1.41, p*=*0.28). However, women who had not received oestrogen treatment or did not continue the treatment up to the age of 45 years were noted to have an increased mortality compared with a reference cohort (HR, 1.84; 95% CI, 1.27–2.68; p=0.001). A meta-analysis(66) reported that the risk of CVD was higher in women who had premature menopause (defined as menopause at <40 years; HR: 1.55, 95% CI:1.38–1.73, p<0.0001), early menopause (defined as at age 40–44 years; HR:1.30, 1.22–1.39; p<0.0001), and relatively early menopause (defined as at age 45–49 years; HR:1.12, 1.07–1.18; p<0.0001), compared with those who underwent menopause aged 50–51 years. Oestrogen has been observed to stimulate vasodilation and maintain endothelial integrity in vascular injury, preventing the development of atherosclerotic plaques(67). Given that atherosclerosis is a chronic process, it is not surprising that early menopause is associated with CVD. Hence, oestrogen might be cardioprotective for women and, therefore, make men more susceptible to CVD.

Thus, overall, men seem to be more susceptible to death from both non-communicable diseases and COVID-19 because they are at a higher risk of underlying CVD, respiratory conditions and other major risk factors for atherosclerosis than women. This increased risk is due to a combination of biological factors, such as the beneficial effects of oestrogen in women, but might also be attributable to an increased incidence of lifestyle and modifiable risk factors in men versus women.

**[H1]The sex gap in health-care utilisation**

The sex gap in COVID-19 is currently making headlines, but, notably, differences in life expectancy according to sex have been reported as early as the 19th century(68) and still persist despite the establishment of focused Men’s Health charities (for example the Men’s Health Forum, which aims to improve both men’s health and male health services(69)) and equality legislation (such as The Equality Act of 2006, which mandated all public health sectors to promote gender equality(70))(71). Globally, men’s life expectancy is 5.1 years lower than women’s(72). A 2018 WHO report highlighted that, within Europe, this gap in life expectancy is due to a higher frequency of premature deaths (deaths occurring between the ages of 30-69 years) as a result of CVD, cancer, chronic respiratory diseases and diabetes(73)(3).

A further contributing factor is the utilisation of health-care services by men. Women attend primary care services more frequently than men but men have been reported to have increased hospital admissions(74)(4). A cross-sectional study of 446 UK General Practices reported that the crude consultation rate was 32% lower in men than women and the greatest sex gap in primary care consultations was seen among patients aged between 16 and 60 years(75).

Although overall admission rates for the NHS within the period 2018–2019 were higher for females than males, when analysis is limited to patients aged between 45–84 (which excludes maternal services) the hospital admission rate for men was marginally higher than women (5,872,710 versus 5,830,144)(76). However, the overall proportion of patients requiring critical care admission was higher in men than women (57% versus 43%)(76).

An Australian survey(77) assessing health attitudes and behaviours of 1,456 adults reported that women were more likely to have their blood pressure checked regularly than men (72% versus 60%, p<0.001) and women were more likely to be aware of the influences of disease prevention strategies, lifestyle and genetics on health (p<0.01). Moreover, women were more inclined than men to pursue advice on disease prevention (94% versus 89%, p<0.001), and more likely to participate in health prevention promotion strategies (p<0.001). A significantly higher number of men than women indicated that they were not interested in receiving information on illness prevention (12% versus 6%, p<0.001). In a US study, Green et al.(78) performed a household interview survey for members of a non-profit health maintenance organisation. This study included 2,603 (1,401 female and 1,202 male) participants and the authors reported that, although women are more likely to report mental (p<0.001) and physical (p<0.001) health symptoms than men, self-reported measures of health concerns were not significantly different. However, women were observed to have significantly higher measures of interest in their health than men (p<0.001).

The QUALICOPC study, which was conducted in Canada in 2013, investigated the health-care seeking practices and behaviours of 7,260 primary care patients. Thompson et al.(79) studied patient experiences as reported in survey questionnaires , finding that women reported they would consult their primary care doctor more readily than men in response to both mental (p<0.001) and physical (p<0.001) concerns. Multiple regression analysis demonstrated that age (p<0.001), trust in their physician (p<0.001), presence of chronic conditions (p=0.001) and patient confidence in their own ability to prevent illness (p=0.001) were significantly associated with increased male medical consultation rates for mental health concerns. However, none of the aforementioned factors were able to predict male medical consultation rate for physical health concerns.

A literature review based on Centers for Disease Control and Prevention data on male health-care utilisation in the USA reported that more men than women (22.8% versus 11.8%) did not attend either a doctor’s surgery, emergency department or have a doctor home visit during 2006. Moreover, women were more likely to attend preventative care visits than men (74.4 visits per 100,000 versus 44.8 visits per 100,000) (80).

Furthermore, The UK bowel screening programme was reported to have a significantly higher female uptake than male (54.4% women and 49.6% of men, p<0.00001)(81) which suggests that men are less likely to engage in health-care programmes than women.

**[H2]Masculinity conventions**

Underutilisation of health-care services by men has been associated with masculinity conventions of self-reliance, strength and control(82) (3), which have also been implicated in high male suicide rates (in 2019, the global age-standardised suicide rate was 12.6 per 100,000 men compared with 5.4 per 100,000 women(83)(84)(73). In a study that performed focus interviews with men to identify attitudes and behaviours to health care, the authors noted that participants did not value health-care utilisation as a “typical” male activity and that many men ignored health issues because they conceived them as a “failure”, disclosure of which demonstrated vulnerability(85). However, the same study also illustrated some divergent views, and some men reported considering health-care initiatives or lifestyle changes as feminine, whereas others had started health-promoting activities (for example, going to rehabilitation sessions). Overall, the consensus in the group was that hegemonic masculinity conventions were intrinsically linked with attitudes to health care, but, overall, insufficient services were tailored for men’s health-care needs, including disease screening.

A separate study, which conducted semi-structured interviews of 6 men diagnosed with testicular cancer in Scotland found that the vast majority of patients did not practice testicular self-examination before their diagnosis , which was attributed to ignorance of the examination process(86). One man was reluctant to seek help when they noticed a testicular lump owing to embarrassment and concerns about feeling foolish if nothing was wrong. Another participant expressed reluctance to seek help because they were afraid to discuss or be examined in a private and sensitive area. Although this study is limited by the small sample size, it does raise some important issues. Many men do not practice testicular self-examination —not necessarily owing to machismo or masculine attitudes, but rather owing to misunderstanding of how to perform the examination. Moreover, many men do not seek help as they fear being embarrassed and vulnerable. Thus, men’s attitudes are not homogenous and many other reasons — rather than simply hegemonic masculinity conventions — might explain an underutilisation of health-care services.

**[H2]Health-care infrastructure**

The infrastructure of the health-care system itself might also be a contributing factor to the underutilisation of health resources. A meta-analysis of 10 studies analysing health-care provider behaviours in medical encounters showed that patient compliance (defined as appointment keeping or compliance with treatment regimen) was positively correlated with the amount of information (general discussion, overview of drugs treatment, procedures and examination and specific details regarding the illness) provided by the health-care provider (p<0.0005)(87). Notably, health-care providers communicated less (Pearson R 0.15, p<0.0005) and provided less information to male compared to female patients (Pearson R 0.22, p<0.01). In accordance with these data, a study(88) using data from the American national ambulatory medical care survey (a survey of visits made to office-based physicians in the USA) observed that females were more likely to receive a general examination and/or medical history (p<0.001), blood pressure check (p<0.001), blood tests (p<0.001) and drugs prescriptions (p<0.05) than men. Interestingly, these trends persisted after controlling for confounding factors such as patient age, diagnosis and illness severity. Furthermore, an assessment of preventive medicine practice amongst 116 primary care physicians showed that only 29% of doctors were likely to instruct male patients to perform testicular exam, compared with 86% who would advise female patients to perform regular breast examination(89). Why these differences arise is unclear and no studies have analysed contributing factors; the causes might be due to physician sex bias, patient requests for care and institutional or societal conventions (for example, a lack of health policies and/or tariffs targeting the male sex or masculinity stereotypes of self-reliance dissuading men from requesting tests and treatments from their physicians) . Further research is needed to clarify the factors causing sex differences in medical care provision; one method of ameliorating these discrepancies would be to target the male sex through specific health programmes.

Unlike women, where sex-specific concerns are handled by gynaecologists, men lack a reference medical speciality that is analogous to gynaecology and do not benefit from gender-specific health-care programmes (such as cervical and breast cancer screening). Andrology services are available only in select hospitals and typically focus on a small number of male-specific conditions, such as erectile dysfunction, male infertility, and testicular cancer. This contrasts with gynaecological services which are present in most hospitals and manage female infertility, lower urinary tract symptoms, ovarian, endometrial and cervical cancer, and a range of disorders related to menstruation, menopause, family planning, sexual dysfunction and sexually transmitted infections. No male-specific screening programmes are run within the UK and, although prostate cancer screening is practised in some countries(90), the diagnostic pathways are variable and can comprise only a PSA blood test and prostate biopsies, despite the publication of both the PROMIS(91) and PRECISION(92) trials that highlighted that non-parametric MRI increases the detection of clinically significant prostate cancer. A EAU white paper on prostate cancer(93) highlighted that the main criticism of prostate cancer screening is overdiagnosis and potentially overtreatment of prostate cancer, but this is a healthcare provider interpretation and there are no large studies on the patient perspectives of overdiagnosis. Therefore, further research is needed to determine whether prostate cancer screening using MRI, PSA testing and prostate biopsies is financially feasible, acceptable to patients and reduces prostate cancer mortality. Given that prostate cancer has the third highest cancer incidence globally and contributed to 3.8% of all cancer deaths in 2020(94), a new approach of detecting early prostate cancer is needed and represents a potential male health screening programme that can reduce male mortality.

**[H2] Health literacy**

The influence of these institutional systems is arguably even more important when we consider that increasing evidence suggests that men have worse health literacy than women. Health literacy is defined as the cognitive and social skills that determine the motivation and ability of individuals to gain access to, understand, and use information in ways that promote and maintain good health(95)(96). A 2007 study assessed health literacy in 759 adults in the UK using a modified Test of Functional Health Literacy in Adults (TOFHLA)(97). The authors observed that higher scores on the health literacy scale were associated with a greater likelihood of eating at least five servings of fruit and vegetables a day (OR: 1.02, 95% CI:1.003-1.03) and non-smokers (OR: 1.02, 95% CI:1.0003-1.03). Men were more likely than women to fall into the limited health literacy category (OR: 2.04, 95% CI:1.16-3.55, p<0.05). A 2015 study included a cross-sectional survey assessing the health literacy of 585 Korean adults using a self-reported health literacy questionnaire. The authors reported that Korean men were more likely to have an inadequate understanding of how to understand and fill out medical forms (p=0.037) and also more likely to have more difficulty understanding the directions on medication bottles than women (p = 0.023). Moreover, women were noted to have a better understanding than men of documentation from a health-care provider (p=0.007). In an indirect measurement of health literacy, a population-based survey of 2216 adults to assess public awareness of cancer warning signs in a British population found that women recognised more red flag symptoms of cancer than men (7.4 versus 7.0, p<0.001)(98).

These studies suggest that men have a lower health literacy than women, which might translate to poorer lifestyle choices with regards to health and also unawareness of potential signs of serious diseases such as cancer. This health illiteracy might be contributing to men’s underutilisation of health services, as they might be unaware of what services are available, the symptoms and signs that would warrant seeking medical advice and the benefits of lifestyle changes and optimisation of morbidities. Thus, one might argue that men are a more vulnerable population than women owing to their health illiteracy and should be targeted to improve their understanding and uptake of health services.

Thus, in addition to the effects of comorbidities and CVD risk factors, men are less likely to use health-care resources than women and this reluctance can be linked to structural barriers, health literacy and personality subtypes. Although male reluctance to use health-care services has been attributed to conventions of masculinity, this theory is an oversimplification and some men do not seek medical care because of fear rather than a show of strength.

**[H2]Intersectional analysis**

Increasing amounts of research is evaluating how social determinants, gendered cultural norms and expectations, and environmental factors can shape male health behaviours and use of health-care services(99)(100)(101)(102)(103)(104). These factors seldom act in isolation; thus, intersectional analysis aims to identify how social, cultural, contextual and identity aspects can affect health outcomes(103). A number of intersectional studies have highlighted how psychosocial factors in conjunction with demographic factors can confer an increased risk of health issues in men. For example, a cross sectional study investigating psychosocial factors associated with HIV risk in men who had sex with men (MSM) illustrates this concept(105). The study involved 2,881 telephone interviews from participants in 4 US cities (New York, Los Angeles, Chicago and San Francisco) and reported that drug use (OR: 2.2; 95% CI: 1.7-2.8, p<0.05) and partner violence (OR:1.5, 95% CI:1.2-1.9, p<0.05) were associated with HIV seropositivity. Moreover, an increased number (odds ratio (OR) for 1 problem 1.8 (95% CI =1.4–2.3), 2 problems 2.7 (95% CI = 2.0–3.6), ≥3 problems 2.2 (95% CI 1.4–3.5, p<0.001) of psychosocial health problems (multiple drug use, depression, childhood sexual abuse and partner violence) were associated with increasing prevalence of HIV infection.A separate study(104) analysed data from 8,490 gay, bisexual and other (those not defining themselves as either gay or bisexual) MSM in Canada. The study investigated associations with demographics and psychosocial factors (specifically recreational drug use, the weekly practice of alcohol binge drinking; suicidal ideation or attempts, anxiety and/or depression necessitating mental health treatment. Multivariable analysis demonstrated a significant association (p<0.05) between sexuality (specifically, identifying as gay rather than bisexual(the authors did not report any associations with the ‘other’ cohort of men); adjusted OR 1.68, 95% CI 1.37–2.05), being ≤45 years old (<30-years: adjusted OR 1.51, 95% CI: 1.27–1.80; 30–45 years: adjusted OR 1.36 95% CI: 1.15–1.63), absence of a university degree (adjusted OR 1.19, 95% CI: 1.02–1.38), a salary of < $60,000/year (adjusted OR 1.32, 95% CI: 1.22–1.554), and presence of two or more psychosocial issues.

However, intersectional analyses have been criticised, because they assume that different factors lie in isolation and are additive when, in fact, they might be intrinsically linked; for example, ethnicity and gender are separate entities, even though both are likely to be contributing together to influence health behaviours(99). Furthermore, some frameworks of intersectional analysis focus on individuals rather than populations or communities and, therefore, the applicability of such data in health policy is questionable(99). Newer intersectional analysis models are emerging (such as the intersectional uniqueness paradigm **[G]**) but these models lack an extensive body of supporting literature(99).

**[H1]Are men inherently vulnerable to infection and mortality?**

Although case numbers of COVID-19 are roughly equal between men and women, mortality rates are higher in men (Figure 1). Both biological and genetic mechanisms could be contributing to the disproportionate male mortality from COVID-19.

*[H2]Immunology*

The mortality rate associated with viral infections in general is higher in men than women(106); this discrepancy has been related to different immunological responses between sexes. Sex differences exist in both the innate and adaptive immune response. Interferon-alpha (IFN-α) is required for immunological defence against viral infections, in which it acts via activation of dendritic cells, stimulation of IFN-γ and activation of both CD8+ T cells and natural killer (NK) cells(107). A sex-dependent pathway has been observed for the induction of IFN-α, whereby production of IFN-α by peripheral blood leucocytes in blood samples from women was higher than in men after stimulation with a TLR7 ligand (p<0.0000001) (107). Likewise, assessment of sex-related differences in cytomegalovirus (CMV) cytokine secretion in healthy CMV-seropositive men and women, revealed that the median interleukin-2 (IL-2) concentration in response to CMV was significantly higher in females than males (60 pg/ml versus 31.5 pg/ml, p=0.001). Furthermore, the female cohort had a higher proportion of responders (patients with an IL-2 concentration >25 pg/ml) — 95% of women and 60% of men (p=0.02)(108).

An in-vitro study reported that cultured peripheral blood mononuclear cells (PBMC) from females stimulated with phytohaemagglutinin produced significantly more B cells (29.6 ± 3.6 versus 23.8 ± 4.3, p<0.05) and total T lymphocyte cells (79.0 ± 1.3 vs 73.4 ± 1.9, p<0.05) than PBMCs from men (109). These data suggest that females produce a greater humoral response than males; this conclusion has been supported by vaccination studies that have observed that women produce higher antibody responses. For example, a study comparing sex differences in response to the influenza vaccination reported that women given the full dose of the vaccine produced higher concentrations of serum hemagglutination inhibition (HAI) antibody than men for all the influenza virus strains(110). Furthermore, the same study observed that women given half the dose of the influenza vaccination produced comparable antibody responses to men given the full dose of the vaccine (25.4 versus 25.6)(110). Similarly, geometric mean titres of HAI after influenza vaccination were significantly higher in females than males (110.7 versus 67.5, p<0.0002)(111). Females have also been shown to produce significantly higher antibody titres in response to the hepatitis A vaccination (p<0.01)(112) and smallpox vaccination (158.5 versus. 124.1 p<0.0001)(113).

[H3] The X chromosome and immunity

The X chromosome encodes genes, such as *TLR7* and *TLR8*, *FOXP3* and *CD40L*, that are involved in recognising viral pathogens, regulation of T cells and immunoglobulin class switching(114). Males possess only one X chromosome, which is inherited from their mother, whereas females carry and express two X chromosomes. The additional X chromosome in women is thought to provide increased immunological protection compared with the single X chromosome expressed in men(115). The X-linked glycosylated 91-kDA glycoprotein gene (*gp91phox*) is subunit of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, which is integral to the production of microbicidal reactive oxygen species (ROS)(116)(117). In a comparison of responses of heterozygous (+/-) mice, *gp91phosx*-deficient mice (-/-) and wild-type mice (+/+) (all female, to control for the confounding effects of sex hormones) to polymicrobial sepsis initiated by caecal ligation and puncture, wild-type animals had the highest mortality (10% overall survival), significantly lower than both mosaic (50% overall survival) and *gp91phosx*-deficient mice (40% overall survival) (p<0.05) (118). The longest median survival time (100 hours) was observed in heterozygous mice, whereas *gp91phosx*-deficient and wild-type mice had a median survival time of 65 hours and 40 hours, respectively. The *gp91phosx*-deficient mice cohort had a significantly higher concentration of circulating blood neutrophil numbers than the wild-type and heterozygous groups (p<0.05) and caecal ligation and puncture resulted in a significant decrease in circulating CD4 and CD8 T-cells in wild-type and *gp91phosx*-deficient mice, but not in the heterozygous mice (p<0.05). Furthermore, sepsis caused a decrease in bone marrow B cells in *gp91phosx*-deficient and wild-type mice but not heterozygous mice (p<0.05). Following caecal ligation and puncture, serum levels of IL-6 were lower in heterozygous and *gp91phosx*-deficient mice than in wild-type animals (p<0.05), but lung concentrations of IL-6 were significantly higher in heterozygous subjects than wild-type or *gp91phosx*-deficient mice (p<0.05). This study highlights how cellular mosaicism for *gp91phox* confers a different immunological response and reduced mortality rate following polymicrobial sepsis compared with wild-type or deficient states.

*Irak1* is another X-linked immunomodulation gene that is involved in regulating inflammatory signalling pathways; data suggest that *Irak1* deficiency is associated with a decrease in sepsis mortality(119). Comparison of mortality rates and cytokine responses in *Irak1*-deficient mice, mice with *Irak1* cellular mosaicism and wild-type mice following caecal ligation and puncture showed that wild-type mice had a significantly higher mortality rate than *Irak1*-deficient and *Irak1*-mosaic mice (p<0.01). Moreover, serum, lung and splenic IL-6 concentrations were significantly lower in *Irak1*-mosaic mice than in wild-type subjects (p<0.05). No statistical differences were observed in bacteraemia among the groups, suggesting that the difference in mortality rates between mice cohorts was related to differences in immunological and inflammatory responses rather than bacterial load. Thus, cellular mosaicism for *IRAK1* related to the presence of 2 copies in females with two X chromosomes might offer immunological protection compared with single X chromosome gene representation.

Taken together, these two animal studies suggest that cellular mosaicism for X-linked genes and, therefore, the additional X chromosome in women, might provide immunological protection.

*[H2]Receptor Expression*

The SARS CoV spike protein binds to angiotensin-converting enzyme 2 (ACE2) receptor on ACE2- expressing cells to facilitate cell entry and viral replication (120)(121). Virus infectivity studies using SARS-COV-2 on HeLA cells showed that SARS-CoV-2 used ACE2 as a cellular entry point in humans(120). Furthermore, anti-serum against human ACE2 inhibited both SARS-CoV-2 and SARS-CoV spike proteins (122). Thus, as ACE2 is probably the entry point for SARS-CoV-2 into cells(1), sex disparities in ACE2 could be clinically relevant. A comparison of serum ACE2 concentrations between sexes in a cohort of patients with heart failure (n = 2022), reported that men had a significantly higher mean serum ACE levels than women (5.38 versus 5.09, p<0.001) and that male sex was the strongest predictor of elevated plasma concentrations of ACE2 (p<0.001) (123). The authors postulated that the higher serum concentrations of ACE2 in men compared with women might explain the sex discrepancies seen in COVID-19 mortality. However, the conclusions that can be drawn from this study are limited, as it only analysed patients with heart failure and did not include patients with COVID-19. Single-cell RNA expression profiling of ACE2 in human lungs from 8 adult human lung transplant donors showed that the two male donors had a higher (albeit not statistically significant) ACE2-expressing cell ratio than the 6 female donors (1.66% versus 0.41%, p= 0.07)(124). However, these data are contradicted by an analysis of five large-scale bulk transcriptomic datasets of normal lung tissue and two single-cell transcriptomic datasets from lung cancer patients, which showed no significant differences in ACE2 gene expression between racial groups (Asian versus Caucasian), age groups (>60 years versus <60 years) and sex (male versus female)(125). Interestingly, data from a rat study that compared lung ACE2 expression between male and female rats at three distinct ages (3 months, 12 months and 24 months) reported no sex differences in ACE2 expression in the 3-month and 12-month cohorts, but a significantly higher ACE2 level in female rats aged 24 months compared with age matched males (p < 0.05)(126) . This difference could reflect an age-related change in ACE2 expression that has not been investigated in humans, which might explain why children are less susceptible to severe disease than adults. For example, a retrospective case series of 2,135 children with COVID-19 reported to the Chinese Centre for Disease Control and Prevention between 16th January 2020 and 8th February 2020 reported that only 6% of cases were severe(127). In accordance with this study a retrospective case series(128) of 1099 patients infected with COVID-19 hospitalised in China between the period 31/12/19-20/01/20, reported that only 0.7% of those diagnosed with severe COVID-19 were aged less than 15 years and the median age of the patient cohort with severe COVID-19 was 52 years.

Smoking status has also been reported to affect *ACE2* expression(125), with higher *ACE2* expression reported in lungs from former smokers compared with non-smokers’ lungs (p=0.04). As men tend to smoke more than women (with a global discrepancy of 35:6), this observation might explain some of the sex discrepancies in COVID-19 mortality(129), whereby a higher rate of smoking in men than women might increase *ACE2* expression and, consequently, increase susceptibility and mortality from COVID-19.

*[H2]Endocrine factors*

Transmembrane protease serine 2 (TMPRSS2) is a cell surface protein that has been shown to be essential for viral entry and replication of the SARS-CoV-2 virus by facilitating the priming of the spike proteins of the virus(130). TMPRSS2 is expressed on the surface of type II pneumocytes in human lung tissue(130) and studies evaluating the transcription of TRMPRSS2 in prostate cancer cells have shown that TRMPRSS2 expression is regulated by androgens and promoted through the androgen receptor (AR)(131). Furthermore, men with castrate levels of testosterone through treatment with either the LHRH agonist leuprolide or oestradiol had significantly lower TMPRSS2 transcripts compared with untreated men (p<0.01)(131).

Thus, androgens have been postulated to contribute to the severity of COVID-19 infection, providing a mechanism by which men are more likely to become severely ill with COVID-19. Astudy of 4,532 men with laboratory-confirmed SARS-CoV-2 infection from 68 hospitals in Veneto, Italy noted that when the data from these patients was considered within the context of the male population of Veneto (2.4 million), 0.2% of men without cancer and 0.3% of men with cancer tested positive for COVID-19. Furthermore, a sub-analysis of this study showed that men with prostate cancer who received androgen deprivation therapy (ADT) had a significantly lower risk of SARS-CoV-2 infection than those not receiving ADT (OR: 4.05, 95% CI:1.55–10.59) or other types of malignancy (OR:4.86, 95% CI:1.88–12.56). These data highlight that androgens could also increase susceptibility to COVID-19 infection, which would make men at increased risk of acquiring the infection.

This hypothesis was supported by data from a murine study, which showed that male mice are at higher risk of mortality from SARS-CoV than female mice(132), in which administration of SARS-CoV led to significantly higher mortality in male mice than female mice (90% versus 20%, p<0.001). Furthermore, ovariectomy of the females significantly increased SARS-CoV mortality compared with intact female controls, whereby 85% of ovariectomised mice died compared with just 20% in the control cohort (p<0.01). These data suggest that oestrogen confers a protective effect against SARS-CoV; extrapolation of these findings to the COVID-19 variant might explain the some of the sex disparities in COVID-19 mortality. However, no studies have examined COVID-19 outcomes in human patients taking hormone therapy, so retrospective analysis of whether COVID-19 differentially effects either women taking oestrogen receptor antagonists or men taking exogenous oestrogen would be interesting.

Evidence suggests that 17β‑­oestradiol regulates many aspects of the innate and adaptive immune systems, including stimulation of pro inflammatory cytokines, increasing neutrophil concentrations and promoting the differentiation of bone marrow precursors cells and monocytes into dendritic cells(133). By contrast, androgens have been observed to suppress the immune system; in vitro studies in cultured macrophages have reported that testosterone reduces the synthesis of TNF-α and nitric oxide by macrophages(134). Moreover androgens have been observed to increase levels of IL-10, which has anti-inflammatory properties and which, therefore, limit the host immune response to pathogens(134)(135). Furthermore, testosterone has been observed to reduce numbers of CD8+ T cells(133). In accordance with these data, men with idiopathic hypogonadotropic hypogonadism have been reported have significantly higher serum levels of the proinflammatory cytokines(136) IL-4 (13.19pg/ml versus 5.33pg/ml, p<0.001) and IL-2 (21.22pg/ml versus 13.01pg/ml, p<0.001) compared with patients with a normal HPG axis (137). Treatment with human chorionic gonadotrophin (hCG) and human menopausal gonadotropin (hMG) in these patients corresponded to an increase in testosterone (1.10pg/ml versus 25.30pg/ml, p<0.001) and significant reductions in IL-2 and IL-4 (<0.001) when comparing pre-treatment and post-treatment levels. (137). In a randomised, single-blind, placebo-controlled crossover trial of testosterone replacement therapy (TRT) versus placebo in 27 symptomatic hypogonadal men (total testosterone 2.2nmol/l)(138), TRT was associated with a decrease in TNFα in patients taking TRT (5.77 versus 2.9, p=0.02) compared with untreated patients.

Other evidence for sex disparities in viral infection related to hormone levels comes from a study that compared sex differences in mice inoculated with herpes simplex virus type 1 (HSV-1) administered into the cornea(139). In this study. the authors observed that HSV-1 periocular and eyelid disease was more severe in male mice and dihydrotestosterone (DHT)-treated female mice than in control female mice (p=0.026). These data highlight that HSV-1-related complications are worse in males than females and that this effect seems to be related to testosterone levels, as females treated with DHT had worse outcomes than control female mice not given this treatment.

A separate study investigated sex differences in mice exposed to the coxsackie B3 Virus (CVB3)(140). Following CVB3 infection, mortality rate or moribund rate that necessitated euthanasia of the animals was significantly higher in male than female mice (50% versus 0%, p<0.01). Furthermore, male mice were reported to have a higher rate of myocarditis than female mice following CVB3 infection (p<0.005), but gonadectomy caused female mice to have a higher rate of myocarditis than males (p<0.00005). Thus, sex hormones might have a role in the development of myocarditis in CVB3 infection.

Collectively, these data highlight that sex differences in hormones can result in altered immunological responses, which might also account for sex differences in COVID-19 outcomes.

**[H1]Effect of COVID-19 on testicular function**

ACE2 has been observed to regulate COVID-19 entering human cells(122)(120) and is highly expressed in the testis. Single cell RNA sequencing studies have demonstrated that ACE2 is predominantly enriched in spermatogonia, Leydig cells and Sertoli cells(141), which suggests that the testis is a potential target for COVID-19 infection; however, no human or animal studies have yet been performed. An initial paper that was posted on the Hubei government’s website and that suggested a link between male infertility and COVID-19 infection(142) has since been criticised as it did not include any clinical data and was purely theoretical. Although speculation around the effect of COVID-19 on male fertility is premature, some (albeit limited) data show that COVID-19 infection in humans might affect the hypothalamic–pituitary–gonadal axis. Comparison of sex hormone profiles in 81 men diagnosed with COVI9-19 at Wuhun Leishenshan hopital with 100 age-matched healthy men(143) showed that COVID-19 infection was associated with an increased level of serum LH than was seen in the control cohort (LH (mIU/ml) median value 5.93 versus 3.28, p<0.0001) (143). Although no significant difference was seen in testosterone levels between the two cohorts, the authors speculated that the increased LH was due to a positive feedback effect of COVID-19 causing reduced testicular function.

Ruan et al.(144) compared the semen analyses of 55 men who had recovered from COVID-19 infection (the median interval between last positive pharyngeal swab RT-PCR test and semen samples collection was 80 days (interquartile range 64–93 days)) with 145 age-matched healthy control patients. The authors reported a significantly lower sperm concentration (66.41 versus 81.34, p=0.0428) and total motility (48.89 versuss 56.38, p<0.001) in those with a history of COVID-19 compared with the control cohort. However, both sperm concentration and total motility for both cohorts were above the WHO recommended reference ranges(145) for these parameters and it is, therefore,unclear whether COVID-19 affects male fertility.

Thus, COVID-19 infection could have longstanding implications for young men of reproductive age.

**[H1]An impetus for social change**

One of the enduring lessons of the pandemic is the way in which it has magnified current health-care inequalities and highlighted the urgent need for reform. Health-care systems — both historically and currently — have failed the male sex. Further investment needs to be made to improve health-care engagement and to target potentially vulnerable populations. Data are available to highlight that men not only have a lower life expectancy but also have a poorer quality of life than women(4); collectively, these factors are likely to be contributing to worse COVID-19 outcomes.

Confronting these political and health-care issues is our professional and ethical duty. Men’s health has been somewhat overshadowed by efforts to improve women’s health, both in health-care policies and in sponsored programmes. For example, The Gates Foundation has a maternal, newborn and child health strategy but no specific strategies related to men’s health(146). And the Gates Foundation gender equality strategy is entirely focused on removing barriers in women and girls’ health, income and education(147)(148). The WHO have developed two global strategies to promote women’s health (“Every Women Every Child “(2010) and “The Global strategy for women’s, children’s and adolescents’ health (2016–2030)(149)) but none specifically targeting men’s health. Moreover, the WHO ‘Gender, health and the 2030 agenda for sustainable development’ seems to be female orientated, as the major health indicators specified include maternal mortality and coverage of essential health services including reproductive and maternal health, but no reference is specifically made to men’s health(149).

This focus primarily on women’s health could, paradoxically, have negative implications for women, as studies have shown that the loss of a husband is linked with both psychological and emotional distress in widows and has adverse effects on physical health, including an increased mortality risk(150). Furthermore, in the USA more than half of all elderly females living in poverty became so following the bereavement of their spouse, illustrating the economic ramifications of premature male death on their female partners (148). Similarly, studies in Australia have reported that widowhood is associated with an increased risk of poverty for women and the UK retirement survey reported that the loss of a partner had negligible effects on income for men but resulted in a decline to 61% of previous earnings for women (151). Indeed, the bereavement of a husband can have implications beyond financial status and in India, widows have been reported to face “social stigmatisation and exclusion”(152) including restrictions to employment owing to caste restraints(152) . Thus, the loss of a husband can result in the loss of the breadwinner in some families and financial and social decline. However, a women’s reliance on a husband for financial and social support suggests sexual inequality and, therefore, this discrimination against women should also be addressed within society.

The process of improving male engagement should be achieved through a structured men’s health-care programme. For example, the Football Fans in Training (FFIT) programme was a randomized controlled trial thatassessed the efficacy of a male-specific weight loss programme in the setting of professional football clubs. The authors reported a significant improvement in the intervention group compared with the control group with regards to blood pressure (mean difference from baseline: −7.50mmHg versus −3.50mmHg, p<0.0001 in systolic pressure and −3.710mmHg versus −3.10mmHg, p<0.0001 in diastolic pressure) and BMI (mean difference from baseline: −1.87kg/m2 versus −0.14 kg/m2, p=0.0003)(153).

The FFIT programme was found to offer sustained beneficial effects and a follow-up study reported that at 3.5 years significant improvements were seen in the intervention group in terms of blood pressure (mean difference from baseline: −3.13 mmHg (95% CI −5.15 to −1.11), p=0.0080 in systolic pressure and −1.56mmHg (95% CI −2.80 to −0.32), p=.0.308 in diastolic pressure) and BMI (mean difference from baseline: −0.96kg/m2 (95% CI −1.31 to −0.60), p<0.001). (154).

In a separate study, a men’s health promotion strategy shaped like a mechanic’s workshop called ‘The Men’s Health Pitstop’ was shown to potentially increase men’s engagement with health care. In this study, a nine-station health assessment programme was developed that was centred around automobiles, for example the mental health station was staffed by a psychologist and the theme was ‘shock absorbers’. The authors observed that 40% of participants had initiated contact with their GP following the Pitstop programme, and 89% had intentions to contact their GP. Furthermore, 57% of the cohort reported making health changes as a result of the programme(155). However, this study included only 315 men who were recruited from an Australian Farming event; thus, the cohort size and demographic mean that extrapolating these findings to the general male population is difficult.

Evaluative evidence regarding men’s health programmes that employ hegemonic masculine stereotypes(155) is lacking, but clearly assuming that all men enjoy sports or cars is naive and a policy centred on masculinity values might, therefore, alienate many men. Further research is needed to identify the most suitable means to engage men and their health; however, specifically targeting and engaging men seems to be good starting platform. The Movember campaign has generated over £346 million to fund over 800 men’s-health-related projects in 21 different countries(156).

National programmes focussed on men’s health have proven successful. Ireland adopted a National Men’s health programme into their health budget, which focused on developing health promotion initiatives to support men to adopt healthier lifestyles(157). The National Men’s health policy and action plan in Ireland developed health promotion initiatives that were sex specific and aimed at optimizing the delivery of health care services with a focus on increasing male engagement. For example, the ‘Farmers Have Hearts’ initiative offered free cardiovascular disease screening and risk factor counselling for men within the rural county of Roscommon in Ireland and resulted in a reduction in the prevalence of hypertension (56% to 40%) and high cholesterol (61% to 39%)(158) in the time period 1st January 2007 to 31st December 2007 (157). Moreover, this programme also included an impetus to produce male-specific health literature and paraphernalia (for example, ‘Men’s Health Matters: A Practical Guide to Healthcare for Men [2011]’) that aimed to educate and address male health issues(157). The National Centre for Men’s Health was created in 2008 to develop and coordinate men’s health research in Ireland and a men’s health training programme was established to optimise engagement of men in both health-care and social services(159). This programme has prompted research into several aspects of men’s health, including male cancers(160) and male depression and suicide(161). Notably, male life expectancy in Ireland has risen a remarkable 6.4 years over the past 21 years(157), illustrating how a men’s health-care programme can be a tangible method to improve the longstanding issue of premature death in men.

Project Brotherhood is a community–academic partnership in Chicago that was developed to address the health and psychosocial needs of African American men(162). The group aimed to provide health services including doctor consultations and public health and development support, such as fatherhood and manhood classes and access to free condoms, in non-medical locations such as gyms and barber shops. The underlying ethos of this community project is to empower African American men through “evidence-based practice, Afrocentric culture integration and a holistic approach to health”(162). Although no scientific data are available regarding the effectiveness of this organisation at improving male health utilisation and outcomes, it highlights a potential holistic model that targets male culture in order to optimize health.

**[H1]The urologist and men’s health**

The WHO defines health as “complete physical, mental and social wellbeing and not merely the absence of disease or infirmity”(163). Thus, premature male death must be approached with a holistic view. Notably, several urological disorders — including erectile dysfunction (ED)— have been associated with a risk of CVD and cancers in men(3), which positions the urologist as a potential gatekeeper of men’s health.

*[H2]Urological disorders as early signs of systemic disease*

Engaging and targeting men with sexual and reproductive health problems might facilitate early diagnosis and treatment of occult disease. For example, erectile dysfunction (ED) is recognised as one of the first signs of occult atherosclerotic disease (164). A meta-analysis of 13 studies comprising 91, 831 participants reported that the relative risk of CVD events in men with ED was 1.44 (95% CI, 1.27-1.63) compared with men without ED(165). The Massachusetts male aging study(166) observed that the incidence rate of ED was 12.4 and 29.8 per 1,000 man-years in men aged 40–49 years and 50–59 years, respectively. Moreover, male infertility might be a proxy for men’s general health (167) — the metabolic syndrome (MetS) is associated with a decreased sperm concentration (p = 0.0026), total sperm count (p = 0.0034), total motility (p = 0.0291), sperm vitality (p = 0.002) and abnormal sperm DNA fragmentation (p = 0.0287)(168). Analysis of the records of 11,935 infertile men demonstrated that men with an abnormal semen analysis had a 2.3 times increased overall mortality risk compared with men with normal semen parameters (HR: 2.9, 95% CI:1.12-4.65, p=0.02) (169). A study comparing the Charlson Comorbidity score (CCI) — a validated predictor of one-year mortality — between 344 men with male factor infertility and 293 age-matched fertile controls reported that the infertile cohort had a significantly higher CCI score than fertile men (0.33 versus 0.14, p<0.001)(167).

Hypogonadism is associated with ED, infertility, diabetes and the metabolic syndrome(3). In a cohort of 294 men who were monitored over a period of 8 years, low levels of total testosterone predicted incident diabetes (OR: 2.7, 95% CI:1.16.6, p=0.03)(170). Moreover, in the TIMES2 study — a randomised, multicentre, international placebo-controlled trial assessing the effects of testosterone replacement therapy in hypogonadal men with diabetes or the MetS(171) — showed that TRT improved glycaemic control compared with placebo (the HbA1c treatment difference (TD): −0.446%, p=0.035). Furthermore, TRT was associated with a significant decrease in lipoprotein A (TD: −0.31 µmol/L, 95% CI:−0.543 to −0.082, p=0.008), total cholesterol (TD: −0.336 mmol/L, 95% CI:−0.558 to −0.114, p=0.003) and LDL cholesterol (TD:−0.210 mmol/L, 95% CI:0.374 to −0.047, p=0.012) compared with placebo. Thus, androgens can both optimise health outcomes (improvements in lipid profiles and glycaemic control) but are also associated with worse outcomes in infection.

A study investigating the relationship between the metabolic syndrome and lower urinary tract symptoms (LUTS) in a cohort of 1,899 American men(172) showed a positive association (OR: 1.68, 95% CI:1.21–2.35) between the MetS in men with mild or severe LUTS (AUA symptom index 2–35) compared with no or low symptoms (AUA symptom index score of 0 or 1)(172). Investigation of the relationship between depression and anxiety and LUTS in a cohort of 14,139 men indicated that men without LUTS had a significantly lower hospital anxiety and depression scale score than those with voiding LUTS (3.3 versus 4.2, p<0.001) or storage LUTS (3.3 versus 3.9, p<0.001). Furthermore, a meta-analysis comprising 11 studies reported that the presence of nocturia was associated with a 1.27-fold increased risk of mortality (RR:1.27, 95% CI:1.16–1.40)(173).

Thus, the urological speciality has a unique opportunity of being able to target major CVD risk factors and other premature causes of male death at an early stage through lifestyle changes, screening for occult disease, risk stratification and early medical intervention. Indeed, screening for CVD in men who present with ED has been shown to be a cost-effective intervention for secondary prevention of both ED and CVD(174)(175). In accordance with these observations, a study of Medicare reimbursement for both CVD risk factors and ED diagnosis and management reported that the cost of CVD risk-factor screening in men presenting with ED was $138.20 per individual and that screening the US population over the duration of 20 years would cost $2.6 billion, but would identify 5.8 million men at risk of CVD, preventing 1.1 million acute CVD events and thereby resulting in a $21.3 billion net saving(175).

Globally, the mortality rate for cancer is almost 50% higher in men than women — global age-standardized mortality rate is 122.7 in men compared with 83.1 in women(176). Men have a higher incidence of all the top five gender-neutral cancers (lung, colon, non-melanoma of skin, stomach and liver) than women, and prostate cancer is the third-most-common cancer worldwide(94) .

Within this context, a large European study(177) of 90,199 participants with 10,455 incident cancers reported that cigarette use was associated with a higher proportion of total cancer burden in men compared with women (30.5%, 95% CI:27.5%-34.3%). Worldwide, smoking is more prevalent in men than women (34) and thus, cigarette cessation is a modifiable risk factor that can be targeted to reduce the incidence of cancer mortality in men.

Notably, infertile men have been observed to have a higher risk of malignancy than fertile men. In a study of data from both a Texas fertility institution and a cancer registry, infertile men had a significantly higher risk of developing cancer (overall rather than specific types) than the general population (standardised incidence ratio (SIR):1.7, 95% CI:1.2-2.5, p<0.05). Moreover, azoospermic men were at a 2.2-times greater risk of developing cancer (overall rather than specific types) than non azoospermic men (HR: 2.2, 95% CI:1.0–4.8, p=0.02)(178). Regarding male cancers specifically, a Danish study investigated the risk of testicular cancer in 32,442 infertile men presenting to a single fertility clinic in Denmark(179). The authors observed that infertile men were more likely to develop testicular cancer than the general population (SIR: 1.6, 95% CI :1.3-1.9, p<0.05).

The pathophysiological mechanisms that underpin this association between male infertility and later cancer diagnosis is unknown, but have been speculated to be related to in-utero exposure to endocrine-disrupting chemicals (EDCs)(180). This theory of testicular dysgenesis syndrome postulates that rising incidences of hypospadias, cryptorchidism, male infertility and testicular cancer are all related to prenatal exposure to EDCs, that result in abnormalities in male sexual differentiation and foetal development(180). However, this theory is limited by a lack of human studies and a paucity of data analysing specific effects of individual EDCs. However, irrespective of the cause, male infertility seems to confer an increased risk of developing malignancy, highlighting that infertile men are a vulnerable population. Thus, urologists have the opportunity to counsel and screen infertile men for symptoms and signs of malignancy that could potentially result in earlier diagnoses and treatment at a less-advanced stage.

*[H2]Men’s health as an early intervention*

In addition to lifestyle advice, a men’s health programme could educate men and screen patients for diseases, including red flag symptoms and signs of malignancy. Indeed, a streamlined urology- centric men’s health clinic could not only offer cancer and CVD screening but also could provide mental health screening, which might help to offset the high suicide rates in young men. In 2018, 6,507 suicides were registered in the UK, of which 75% were men(181). Moreover, the global suicide rate in the age group of 15–19 years was 2.6 times higher in males than in females(182). Although trials assessing the effects of early interventions in suicide prevention are lacking, a Cochrane review of 55 trials reported that cognition-based psychotherapy resulted in fewer participants repeating self-harm than conventional treatment (OR: 0.70, 95% CI:0.47-1.30). Given that a history of self-harm is a major risk factor for suicide(183), early psychological intervention might help reduce the high burden of male suicidal death — if urologists can identify these patients during their consultations, early referral to support system could be arranged.

The urological speciality is the only medical discipline that deals with male-specific benign and malignant diseases, and male sexual and reproductive health is strongly associated with the major causes of premature male death(3). Within this context, urologists are in an ideal position to become the gatekeepers of men’s health.

**[H1]A new model for men’s health**

Within both publicly funded health-care frameworks (for example, as in the UK) and systems combining public and private funding (such as in Australia and the USA), after assessment by the primary care provider, patients often need to consult with multiple specialists for each individual health complaint

This approach is resource heavy for primary and secondary health providers and time-consuming for the patient. Moreover, it might also contribute to men’s reluctance to seek health care(75). Thus, a more holistic approach is required, using male-specific diseases as a platform to target men’s health in general and to improve health outcomes. Accordingly, we should consider and offer health screening for occult disease in a more systematic approach and at an earlier age than is currently implemented. For example, men presenting with ED should be screened for CVD risk factors immediately, owing to the strong association between ED and subsequent CVD events(165) and, conversely, those men who have CVD risk factors should be assessed for sexual dysfunction. Depression and sexual dysfunction have a bidirectional relationship(184); thus, men presenting with low mood or ED should be screened and, if necessary, treated for both. Moreover, men presenting with infertility should be assessed for hypogonadism and symptoms and signs of malignancy(3). All men should undergo a CVD risk factor assessment, as treatment of modifiable and lifestyle risk factors can reduce the risk of future CVD events, malignancy, ED and infertility.

Qualitative studies using patient questionnaires in a range of specialities have suggested high patient satisfaction with ‘one-stop’ clinics compared with traditional outpatient encounters(185)(186). A study investigating patient experiences with a one-stop haematuria clinic and a clinical pathway containing several visits showed high patient satisfaction (recorded through a questionnaire), reporting that 82% of the participants expressed preference for a one-stop clinic model(185). A separate study(186) investigated the effects of a one-stop clinic for minor skin surgery in 32 UK plastic surgery departments, reporting that the use of one-stop clinics was associated with a higher degree of patient satisfaction (95% versus 72%) than conventional pathways and improved 18-week waiting time targets compliance (95% versus 85%).

Thus, one-stop men’s health clinics might improve patient satisfaction and male uptake of health-care services.

*[H2]COVID-19 as an opportunity*

The COVID-19 pandemic has forced rationalisation and prioritisation of clinical services. Elective surgical output has been universally reduced, with a focus on oncological operations and life-saving surgery. A description of the activities of the urological department in Bergamo Hospital, Italy, at the beginning of the pandemic highlighted that, in March 2020, the operating capacity was reduced to 15% of the normal activity and focused solely on oncological and emergency procedures. Moreover, 30% of the urological staff were redeployed to care for COVID-19 patients and 7 of the 13 urologists remaining were self-isolating(187). This report highlights the challenges presented by the COVID-19 pandemic, both in terms of service provision and retention of the workforce. Notably, specific recommendations from the European Association of Urology (EAU) focussed on response to the coronavirus pandemic have categorised the overall management of sexual health and ED in the COVID-19 period as low priority(188). Although this approach might be justified in view of the immediate risks associated with COVID-19 infection compared with the benefits of andrological treatment, the long-term ramifications of delays in treatment, notwithstanding the effects on patients’ mental health, are not clear. Indeed, both ED and infertility are harbingers of underlying serious health risks and provide opportunities to mitigate risk factors at an early stage to avoid their long-term sequelae. Given the current prioritisation of oncological procedures, the post-pandemic period will probably require re-organisation and re-structuring of many clinical services to cope with demand, possibly to the detriment of subspecialities dealing with benign conditions such as male sexual and reproductive health(188). However, we believe that this period presents an opportunity to develop a dedicated men’s health programme aimed at assessing and managing a range of health issues in a single visit, and that could be implemented worldwide.

Indeed, men’s health services are lacking worldwide. In a Delphi survey of men’s health for 128 stakeholders (policy makers, clinicians, researchers and consumers) from 28 Asian countries(189), only 20.4% of respondents described men’s health being present in one or more of: national policy, public awareness programmes, health-care services, clinical practice guidelines, health screening programmes, training for health-care workers, school health education, research, social support service, national registries or law. Moreover, 85% of participants were concerned about men’s health issues, specifically smoking, hypertension and cardiovascular disease.

Establishing a men’s health programme will require collaboration from a range of specialities, including urologists, cardiologists, endocrinologists, dieticians, physiotherapists and psychologists, and would not only benefit patients but could also streamline services in a cost-effective manner(8). The contribution of primary care practitioners will be paramount to the success of such a programme, and a shared-care management approach with urologists would enable ongoing treatments and preventative care practice in the community. Future data acquisition will enable the development of evidence based, sex-specific protocols and guidelines, facilitating a community men’s health programme supported by primary care doctors.

A structured men’s health-care programme could also improve health-care utilisation by appealing to the male psyche and promoting men’s empowerment over their health. The implementation of this approach might vary according to race and ethnicity. For example, data are available to show that the Latino culture values men as the breadwinner or provider for the family(190); thus, this community could be encouraged to support men’s health with the rationale that it can be instrumental to the wellbeing of individual families and the community as a whole. Similarly, studies have reported that dietary interventions instituted through African American churches can improve fruit and vegetable intake for African American Men(191)(192). Thus, churches could provide an ideal location to advertise and practice men’s health care initiatives to target the African American community. Men’s health awareness campaigns can be regularly promoted around Fathers’ Day, Men’s Health Month (June) and other high-profile campaigns, such as Movember.

The intersectionality of sex, gender, race and health outcomes is a complex but expanding field of research and the benefit of a men’s health programme would be the opportunity to collect sex-specific data. A 2019 bibliometric analysis of sex-related reporting in medical research studied more than 11.5 million papers published between 1980 and 2016, and observed that sex-related outcomes reporting increased from 36% to 69% and 59% to 67% in public health and clinical medicine research, respectively(193). Thus, although sex-specific outcome reporting is improving, the literature is still lacking.

Psychological input will be mandatory for developing any men’s health programme, because our lack of understanding of how to change the patterns of thinking or behaviours of men to embrace health promotions and improve health literacy is a barrier to optimising health outcomes (194) (195). Moreover, sociological data acquisition could also optimise male utilisation of health-care services, helping to identify and address societal, cultural, and ethnic determinants affecting healthcare(195).

*[H2]Challenges and lessons*

Developing a new model of care will have initial challenges, including acquisition of funding and the logistics of setting up a multidisciplinary service. However, the sex discrepancies in COVID-19 mortality rates, coupled with the sex gap in life expectancy from non-communicable diseases, has highlighted that the current health-care system has failed men. A novel perspective on men’s health is required. One programme attempting to address this failure is the EAU working panel on Male and Sexual Reproductive Health, which has developed the first evidence-based guidelines on male sexual and reproductive health, including guidance on how urological conditions can be harbingers for occult systematic diseases(174).

A men’s health service would enshrine and enable pooling of services and resources, expedite patient access to care, and could also facilitate referral for specialist investigations or treatments, such as cardiac angiography, treatment of diabetes, imaging for raised PSA. Alternatively, these investigations could even be incorporated into current streamlined pathways, for example MRI imaging and same-day local anaesthetic prostate biopsy for rapid access prostatic cancer diagnostic pathways. A one-stop model could reduce treatment delay, improve cost-effectiveness and increase patient satisfaction(10). Moreover, a sex-specific health-care model would incorporate sex-specific protocols, patient-reported outcomes and a patient-centred environment that could facilitate interaction with peers(4), facilitating disease screening and dissemination of health information to patients. Moreover, auditing of the service and patient experiences would provide an opportunity for research into men’s health. This model would be dynamic, incorporating patient opinions in order to constantly adapt to optimise patient satisfaction and clinical outcomes.

The creation of a programme like this could also be used to trial new and emerging technologies to identify novel methods of improving male health-care outcomes. For example, the mobile web application, ScreenMan, which provides educational information for 15 health conditions including depression and alcohol misuse. In an evaluation of the usability of the software through a participant questionnaire using a validated system usability score (SUS), ScreenMan was categorised as having a ‘good’ SUS score (mean 76.4), but no statistically significant improvement was seen in behavioural change patterns in favour of participants intending to screen for medical conditions earlier (<6 months) following the use of the software(196). Although this app did not change health-care outcomes, others could be evaluated and might be helpful for implementation within a men’s health programme.

A men’s health programme would provide the opportunity to implement new technologies to optimise existing health pathways. New technologies, such as telehealth (telecommunication medicine),could potentially improve male engagement by removing time and location restraints to health-care services and also prove a cheaper, less labour-intensive resource(196). A systematic review analysing the impact of telehealth in urological conditions observed that the majority of studies reported clinical safety and high patient satisfaction with telehealth compared to standard pathways(197). Thus, telehealth should have a role in the implementation of a new approach to men’s health.

**[H1]Conclusions**

The disparity in increased COVID-19 mortality between men and women has highlighted underlying deficiencies in our current health-care system. Men are more vulnerable to infections than women owing to underlying biological causes, including immunological(106), hormonal(133) and genetic differences(198), and men also tend to have poorer general health and reduced access to health care. This discrepancy has also resulted in a sex gap in life expectancy from non-communicable diseases(3). Policy makers and health-care stakeholders must take heed of the success of FFIT and Ireland’s men’s health programme and develop approaches that specifically and aggressively target men, especially given their reluctance to engage with health-care services and the higher rates of health illiteracy in men than women.

The resumption of normal health-care services once the COVID-19 pandemic has resolved is likely to be followed by a high burden of referrals; thus, development of a new model of care within a streamlined multidisciplinary setting is a logical approach to create focused men’s health clinics that could solve the problem of sex discrepancies in health and disease.

Figure 1 |Sex-disaggregated cases, hospitalisations, intensive care admissions and deaths in COVID-19.

Figure 1 demonstrates that the number of confirmed cases of COVID-19 is similar between sexes (49% vs 51%) but men have a higher rate of hospitalisations, intensive care admissions and deaths.

*Data source: Global Health 5050.* [*https://globalhealth5050.org/covid19/*](https://globalhealth5050.org/covid19/)*. Accessed: 05/10/2021.*

Figure 2 | Obstacles and benefits of men’s engagement with health-care services. (a) current barriers to male health-care utilisation, include the absence of a reference specialist and the need to see several specialities, sometimes in different hospitals and over multiple appointments. (b) Advantages of a men’s health policy include a multidisciplinary pathway that incorporates the diagnosis, treatment and prevention of both benign and malignant conditions. (c) Potential outcomes from a men’s health policy (such as increasing male life expectancy, novel data acquisition and reducing the burden and costs of cancer and cardiovascular disease morbidities through a preventative medicine approach.

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