ASSESSMENT OF PERSONAL VULNERABILITY TO COVID-19

Sources of evidence and methods leading to adopted risk estimates

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OVERVIEW

This report describes the sources of evidence underpinning the assessments of vulnerability in Table 1 of our guidance, and the methods by which adopted estimates of risk were derived. It is divided into three sections.

The first section outlines our overall approach, and summarises the main sources of evidence that have been used. The second describes the derivation of risk estimates for specific risk factors. The third sets out the methods used to translate estimates of relative risk into a more naturally interpretable measure that can be summed across risk factors to give an overall indication of personal vulnerability to Covid-19.

We aim to provide the best assessments of risk that are possible from available data, but inevitably, there are scientific uncertainties. New evidence may sometimes indicate that an earlier risk estimate was sub-optimal, and should be modified. The guidance on vulnerability is therefore periodically updated and refined as relevant new evidence become available. To make clear how this process has occurred, in each section of the report, we first describe the methods used in our initial assessments of risk (as at 20 May 2020), and then report on findings at successive updates, and any changes in adopted risk estimates that have ensued.

SECTION ONE: OVERALL APPROACH AND SOURCES OF EVIDENCE

INITIAL ASSESSMENT: 20 MAY 2020

We wished to assess and compare risks of fatality in people who contract SARSCov-2 infection, according to their age, sex, ethnicity, smoking habits, and various comorbidities. In preliminary searches of the published literature, no evidence could be found on risks of fatality in representative samples of all people infected by the virus (including those with asymptomatic infection). However, analyses of mortality from Covid-19 in the general population could be expected to provide good proxy measures of relative risk, provided the likelihood of contracting infection did not vary importantly according to the risk factors under consideration (for example because of selective shielding by people with certain comorbidities). In addition, estimates of risk might be possible by combining data on fatality rates by comorbidity in patients admitted to hospital because of Covid-19 with information about the prevalence of comorbidities in such patients as compared with the general population.

Because of the urgency to improve on earlier advice, which necessarily was based largely on consensus of expert opinion, we initially sought reports that would provide the strongest scientific evidence relevant to the UK, without attempting systematically to search for, and review, all published evidence that might bear on the risks that we were trying to characterise. In this respect, one paper stood out as particularly suited to our purpose.

That report, from the OpenSAFELY (OS) collaborative, presented first results from a cohort study of more than 17 million adults registered with English general practices and followed up from 1 February 2020 to the earlier of death or 25 April 2020 [1]. Multivariate Cox regression was used to estimate mutually adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for death in hospital with confirmed Covid-19 (ascertained by linkage to a national notification system) in relation to risk factors ascertained from pseudonymised individual primary care records. Data on other deaths in the cohort (needed for censoring of follow-up) were obtained by linkage to data held by the Office for National Statistics (ONS). A secondary analysis, which censored follow-up at 6 April 2020, allowed exploration of the possibility that HRs for some comorbidities in the main analysis underestimated vulnerability because, in response to advice from the UK government at the end of March, people with those diseases had selectively shielded themselves from exposure to infection. As well as sex, age, ethnicity, smoking habits and multiple comorbidities, analyses adjusted for deprivation (using an index graded to five levels) and for the administrative region of the patient's general practice (to allow for varying rates of infection in different parts of the country).

This study had unique strengths. It included a substantial proportion of the adult population nationally, and was based on more than 5000 deaths attributed to Covid-19. Moreover, information about risk factors came from data recorded before the onset of infection, reducing the potential for bias in relation to the outcome. Limitations included restriction of the outcome to deaths in hospital (some cohort members may have died from Covid-19 elsewhere), and incomplete data on some risk factors (although the extent of missing

information was generally small). A further limitation when applying its findings in our risk model was that some of the categories of comorbidity which it analysed were heterogeneous. For example, chronic pulmonary disease aggregated chronic obstructive pulmonary disease (COPD) of varying severity with other lung diseases such as cystic fibrosis and bronchiectasis; and there was no distinction between Type 1 and Type 2 diabetes.

These weaknesses do not detract seriously from the value of the OS study. Nevertheless, it was important to check the plausibility of its findings, using data from other studies. This was done using several independent sources of information.

The ONS has published data on mortality from Covid-19 (as the underlying cause of death) by sex and age in England and Wales during March 2020 [2]. These death rates make no allowance for effects of comorbidities, the prevalence of which may vary by age, and between men and women. However, they provide a benchmark against which more fully adjusted estimates of relative risk by sex and age can be compared.

Another useful resource was a report from the ISARIC study on outcomes, including mortality, in a cohort of 16,749 patients with Covid-19 admitted to hospitals in England, Wales and Scotland during 6 February 2020 to 18 April 2020 (28% of all such admissions nationally during that period) [3]. Within the cohort, 49% had been discharged, 33% had died, and 17% continued to receive care at the date of reporting. The prevalence of various comorbidities in the cohort was explored, and multivariate Cox regression was used to explore risk of death in relation to age, sex and selected comorbidities. An important limitation was the ascertainment of comorbidities from clinical records, which is unlikely to have been complete or uniform across the cohort.

Data were also available on the prevalence of comorbidities by sex and age in samples of people (intended to be nationally representative) from recent rounds of the Health Survey for England [4-7]. Although these data predated the ISARIC study, were only from England, and did not apply the same diagnostic criteria and methods of ascertainment, they could be used to calculate an approximate predicted prevalence of comorbidities in the ISARIC cohort. Comparison of the observed and expected prevalence then gave an indication, albeit crude, of the age- and sex-adjusted relative risk of being hospitalised with Covid-19 according to comorbidities. When combined with HRs for death following admission to hospital, this allowed approximate estimation of relative risks of mortality from Covid-19 among people with the comorbidity in the general population.

Plans for further investigation

We recognise that the checks which we have carried out on the plausibility of risk estimates from the OS study, are limited in scope, and that further reports, of varying degrees of relevance and importance, have still to be identified and reviewed. We intend to undertake this task more systematically over the next few months. In addition, further reports are expected on the OS study, and on another similar but smaller dataset. Findings from such reports will be reviewed as they become available, and risk estimates revised if the balance of evidence has changed. In particular, we hope that evidence-based risk estimates may become possible for more specific sub-divisions of some of the categories of comorbidity.

UPDATE 1: 26 MAY 2020

In the interval since this report was first compiled, an updated version of the ISARIC report has been published following peer-review [1.1]. Changes included extension of recruitment and follow-up, so that analysis was now based on 20,133 hospitalised patients. By the end of follow-up, 8,199 (41%) had been discharged alive, 5165 (26%) had died, and 6769 (34%) were still receiving care.

In addition, two important new papers have been published [1.2, 1.3], which focus principally on diabetes, but provide information also about other risk factors. They report on related population-based cohort studies, one of all patients registered with English general practices, and the second of the subset of that population with a registered diagnosis of diabetes.

In the first study (by Barron and colleagues [1.2]), a cohort of more than 61 million patients (all ages) who were registered with English general practices at 19.2.20, were followed for deaths from Covid-19 in hospital during 1 March to 11 May of that year. The main focus was risks associated with different types of diabetes, information about which was ascertained from a database (the National Diabetes Audit (NDA)), updated in 2018/19, which abstracts data from general practice and specialist records. The cohort included 263,830 patients with Type 1 diabetes, 2,864,670 with Type 2 diabetes, and 41,750 with other forms of the disease including maturity onset diabetes of the young. Information about other risk factors, and on deaths in hospital from Covid-19 (n = 23,804), was obtained by linkage to other national datasets. Multivariate logistic regression was used to estimate odds ratios for cumulative mortality from Covid-19 over the study period in relation to age, sex, ethnicity, social deprivation (five levels), region (seven categories), diabetes (broken down by type), and in some analyses, coronary heart disease, cerebrovascular disease and heart failure.

The investigation differed from the OS study in several notable ways.

- Although the cohort will have included members of the OS cohort, it was substantially larger and extended to children as well as adults
- Follow-up was for longer, and from 28 April, deaths from Covid-19 included some in which the diagnosis was made on clinical grounds, but without confirmation by testing
- Ascertainment of comorbidity was limited to diabetes and cardiovascular disease, and did not include BMI or chronic kidney disease, both of which are related to diabetes
- Ethnicity was determined from a different source (the Bridges to National Population Segmentation dataset)
- Diabetes was ascertained from the NDA

The second new paper (Holman et al. [1.3]) describes an investigation of risk factors for death related to Covid-19 (i.e. in which Covid-19, with or without confirmation by testing, was registered as the underlying or a contributing cause of death) among cohorts of patients in England with Type 1 (n = 265,090) and Type 2 (n = 2,889,210) diabetes, identified from the NDA. During follow-up to 1 May 20, there were 9,795 such deaths, including 9,341 in which Covid-19 was recorded as the underlying cause. For this analysis, which was restricted to

patients with diabetes, data were available on a wider range of risk factors, including also most recent HbA1c level as a measure of diabetic control, estimated glomerular filtration rate (eGFR) (recorded between 1.1.19 and 31.12.20), BMI (from measurements during 2017-19), smoking habits, and prescribed treatment for hypertension. Analysis used multivariate Cox proportional hazards to estimate HRs.

Despite the overlap of these new cohort studies with the OS study sample, they provide important new information. In particular, we have used them to check on several risk estimates from the OS study, to generate risk estimates for a finer classification of diabetes by type and level of control, and to explore our assumption that relative risks for diabetes multiply those from other risk factors when they occur in combination.

A description of those checks and additional risk estimates is included in the assessments of evidence on specific risk factors.

UPDATE 2: 10 JUNE 2020

In the interval since the last update, we have identified several further papers that bear consideration.

The first report describes a national analysis of hospitalisation and mortality in the first 9,159 cases of Covid-19 confirmed by PCR testing in Denmark [2.1]. Diagnoses were made during 27 February to 30 April 2020, and cohort members were followed for mortality with censoring at the earlier of May 15 or 30 days after their first positive PCR test. In a multivariate logistic regression analysis, odds ratios for mortality were estimated according to age sex and various comorbidities. For our purposes, the evidence from this investigation is not as strong as that on which our risk model currently is based – it comes from a different country; selection for PCR testing, the criteria for which changed over the study period, may have rendered the cohort unrepresentative of the wider population in some of the associations of mortality with risk factors; and risk estimates for comorbidities were not so fully adjusted. Nevertheless, it offers some support regarding the relative importance of different risk factors. Thus, risk was higher for diabetes where it was treated with insulin (OR 2.0 vs. 1.3 for other glucose-lowering drugs), higher for heart failure (OR 1.7) than for ischaemic heart disease (OR 1.2), relatively high for hospital-diagnosed kidney disease (OR 2.0), and higher for organ transplantation (OR 2.7) than for almost all of the comorbidities examined. Interestingly, the highest risk was for major psychiatric disorder treated by antipsychotic drugs (OR 3.6, 95% CI 2.5 – 5.2), a factor on which data from the UK are not yet available. For hypertension, the OR was 1.3 (95%CI 1.1-1.7), which supports the view that after adjustment for other factors (less complete in this investigation than in the OS study [1] or that by Holman and colleagues [1.3]) any risk from the disorder as a whole is likely to be fairly small (this does not preclude the possibility of a higher risk in one or more sub-categories of hypertension). On balance, we do not think the findings of this Danish study provide grounds for changing our adopted risk estimates.

Using a publicly available national dataset, Giannouchos and colleagues have used multivariate logistic regression to assess risk factors for adverse outcomes (intensive care unit admission, mechanical ventilation or death) in 89,756 people in Mexico who tested positive for Covid-19 [2.2]. Applicability of the findings to our risk model in the UK is limited for several reasons. The ethnic mix of the study population was different; the outcome was not restricted to death; indications for testing may have not have been completely standardised, raising the possibility of bias in risk estimates; and the stratification of age was crude (with only three levels, one of which was children). Therefore the results do not warrant any changes in our adopted risk estimates. They do, however, support the view that smoking is not an important determinant of vulnerability, and that any overall risk associated with hypertension is small.

A case-control study among beneficiaries of the regional Health Service in Lombardy, Italy, included a comparison of 617 cases with critical (requiring assisted ventilation) or fatal Covid-19 and 2,969 controls, matched for sex, age and community, from the general population [2.3]. After adjustment for several comorbidities and other medication, there was no significant elevation of risk in relation to prescription in the previous calendar year (2019) of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs),

calcium-channel blockers, diuretics or beta-blockers. The highest OR (1.15, 95%CI 0.91-1. 44) was for calcium-channel blockers.

Another paper describes characteristics associated with hospitalisation in a series of 600 Covid-19 patients with rheumatic diseases from 40 countries [2.4]. The most common of the rheumatic comorbidities in the study sample were rheumatoid arthritis (38%), SLE (14%), psoriatic arthritis (12%) and axial and other spondyloarthritis (8%). Forty six percent of patients were admitted to hospital. After adjustment for age (in two strata), four types of comorbidity, smoking (ever vs. never), and rheumatic disease diagnosis, the risk of hospitalisation was elevated in patients treated with glucocorticoids equivalent to ≥10 mg/day of prednisone (OR relative to no corticosteroids 2.05, 95%CI 1.06-3.96). However, in those treated by biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), alone or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), risk was lower than in those receiving no DMARDs. There was a suggestion of higher risk in patients with SLE as compared with rheumatoid arthritis (OR 1.80, 95%CI 0.99-3.29).

As a source of evidence for our purposes, this report has several major limitations. The data come from multiple countries, and relationships between variables cannot necessarily be extrapolated to the UK. There is no clear statement of the criteria by which potentially eligible patients were selected for inclusion in the case series. Their high rate of hospitalisation suggests that they were not typical of all Covid-19 patients with rheumatic diseases, and it is possible that decisions to enrol them were influenced by their clinical course after Covid-19 was diagnosed. The outcome was hospitalisation rather than mortality, and because its prevalence was high, ORs will have been further from the null than corresponding relative risks. For example, with an overall 46% of patients admitted to hospital, a crude OR of 2 in the 64 patients using high doses of corticosteroids as compared with the 403 not using corticosteroids would correspond to a relative risk of only 1.4. Also, control for potentially important covariates was limited – for example, only two strata of age were distinguished. For these reasons, the data cannot be used to refine our adopted risk estimate for rheumatic diseases. They do, however, suggest that among people with inflammatory arthritis, risk may be higher in those treated by high doses of oral corticosteroids, while there is no additional risk from use of b/tsDMARDs.

Five further papers were judged to provide no evidence of note in relation to our estimates of risk [2.5-2.9].

UPDATE 3: 29 JUNE 2020

New publications identified since our last report do not provide a basis on which to change the adopted risk estimates in our model, but several provide information that is relevant to the assessment of vulnerability to Covid-19.

Most notable is a paper in which McKeigue and colleagues report a matched case-control study of 2,755 patients in Scotland with severe Covid-19 (i.e. leading to intensive care or death within 28 days of a first positive test for the disease), who were diagnosed up to 13 May 2020 [3.1]. Each case was compared with seven controls, of the same sex and age, who were selected from the population register of the same primary care practice. Previous comorbidities and treatments were ascertained from diagnostic codes for hospital admissions in the past five years and prescription records over the past 9 months. In addition, diabetes was determined by linkage to a national database. Associations with risk factors were assessed by conditional logistic regression. The mutually adjusted ORs that were estimated are not directly comparable to the HRs in the OS study because the range and specification of the variables included in the regression models differ. For example, the multivariate analyses by McKeigue and colleagues aggregated chronic kidney disease with having received a transplant, and included residence in a care home as a covariate, as well as receipt of any prescribed medicine in the past 9 months, and any hospital admission in the past five years, but not ethnicity or BMI. For this reason, and also because of the smaller sample size, we do not think that the risk estimates are sufficiently different from those that we have adopted to call them into question.

It is, however, notable that for most comorbidities, risk estimates were higher when analyses were restricted to participants aged < 60 years (Table 3.1). This may in part reflect differences in case-mix. For example, among the category “chronic kidney disease or transplant recipient”, there may have been proportionately more transplant recipients at younger ages. Nevertheless, the finding suggests that for some comorbidities there could be important interactions between age and other risk factors, and that our current model, which is based on analyses for all adults, may underestimate relative risks in people of working age. We hope that further analyses of the OS or similar cohorts, restricted to working ages, will soon become available. Meanwhile, the finding emphasises the need for caution in interpretation of our adopted risk estimates.

Table 3.1 Odds ratios from multivariate analyses of case-control study by McKeigue et al stratified by age

Risk factor	Age <60 years		All age groups	
	[a]OR	(95%CI)	[a]OR	(95%CI)
Type 1 diabetes	3.20	(1.61-6.35)	2.19	(1.41-3.42)
Type 2 diabetes	2.53	(1.79-3.57)	1.62	(1.44-1.81)
Other/unknown type diabetes	3.35	(0.75-14.99)	1.70	(0.91-3.19)
Ischaemic heart disease	0.97	(0.57-1.62)	1.10	(0.97-1.24)
Other heart disease	1.81	(1.21-2.72)	1.39	(1.24-1.55)
Asthma or chronic airway disease	1.58	(1.20-2.08)	1.54	(1.39-1.71)
Chronic kidney disease or transplant recipient	17.7	(4.3-73.6)	4.27	(2.94-6.21)
Neurological (except epilepsy) or dementia	4.04	(2.41-6.78)	1.98	(1.73-2.27)
Liver disease	4.30	(1.60-11.57)	2.17	(1.38-3.40)
Immune deficiency or suppression	0.86	(0.30-2.52)	1.30	(0.82-2.08)

[a]Risk estimates are adjusted also for residence in a care home, any prescription in past nine months and any hospital admission in past five years

In addition to the paper by McKeigue et al, other recent papers report on risks of death by ethnicity in patients admitted to British hospitals with Covid-19 [3.2,3.3], risk of hospitalisation for confirmed Covid-19 by ethnicity in the Biobank cohort [3.4], relative risks of Covid-19-related mortality among sub-cohorts of the OS study sample with COPD and asthma according to their use of inhaled corticosteroids [3.5], risk of mortality among cancer patients with test-positive Covid-19 according to recent treatment [3.6], relative frequency of severe outcomes in Covid-19 patients with different types of rheumatic disease and with no rheumatic disease [3.7], and estimated infection fatality rates in Belgium [3.8]. Relevant findings from these investigations, and the conclusions that we draw from them, are set out in the sections that follow on specific risk factors and estimation of individual vulnerability.

Two other papers were reviewed, but did not impinge on our assessment of risk [3.9,3.10].

UPDATE 4: 16 JULY 2020

The most telling new publication since our last update describes an updated analysis of the OS cohort [4.1], which differs in several ways from the analysis that was previously reported.

Most important is a substantial increase in the number of Covid-19 deaths that were analysed (10,926 as compared with 5,683). This is attributable in part to slightly longer follow-up (up to 6 May), but mainly to inclusion of all deaths in which confirmed or suspected Covid-19 was mentioned anywhere on the death certificate, irrespective of whether death occurred in hospital or elsewhere (ascertained through linkage with ONS data). The extra deaths occurred disproportionately at older ages and in women.

In addition, the cohort was slightly smaller (17,278,392), mainly because patients with missing data on social deprivation were excluded. There were also a few refinements in the specification of several risk factors. In the main analysis, chronic renal failure was graded to two levels, and a secondary analysis assessed risk in relation to a history of kidney dialysis or end-stage renal failure. Brain tumours appear no longer to have been included in "Other neurological disease", and secondary analyses examined more detailed associations with ethnicity and interactions between hypertension and age.

As a consequence of these changes and additions, there were some notable changes in the results. The increase in risk with age was a little steeper (a relative risk of approximately 2.8 for each additional 10 years in the fully adjusted analysis). The relative risk for men as compared with women was reduced (1.59, 95%CI 1.53-1.65), although interestingly, it was higher in a sensitivity analysis with follow-up censored at 6 April 2020 (HR 1.90, 95%CI 1.75-2.05). It is unlikely that this difference can be ascribed to random sampling variation, and it suggests that as the epidemic evolved, levels of exposure in men relative to women may for some reason have reduced. Some risk estimates by ethnicity were slightly lower, as were those for obesity, asthma and several other comorbidities, although this may in part reflect a greater effect of selective shielding with more prolonged follow-up. The HR for liver disease was somewhat higher.

The implications of the new findings for our adopted risk estimates are discussed in Sections 2 and 3.

A second new paper describes a case-control study in London, comparing 872 inner city residents admitted to hospital with confirmed Covid-19 and 3,488 community controls matched for sex and age [4.2]. After adjustment for deprivation and comorbidities, admission for Covid-19 was significantly associated with black but not Asian ethnicity (ORs 2.28, 95%CI 1.87-2.79, and 1.20, 95%CI 0.86-1.66 relative to white ethnicity). The paper also reports a linked cohort study of 1,827 adults consecutively admitted to hospital with Covid-19. Age, male sex, and Asian (adjusted HR 1.54, 95%CI 0.98-2.41 vs. white) but not black (adjusted HR 0.84, 95%CI 0.63-1.11) ethnicity were associated with in-hospital mortality. These results are broadly consistent with our currently adopted risk estimates for black and Asian ethnicity.

Two papers present data that bear on estimation of absolute case-fatality rates corresponding to Covid-age (see Section 3). The first, which applied a mathematical model

to data on 191,392 laboratory-confirmed Covid-19 cases and 201,141 confirmed and probable Covid-19 deaths in New York city residents during 1 March to 16 May 2020, estimated infection fatality rates (IFRs) of 0.12%, 0.94% and 4.67% at ages 25-44, 45-64 and 65-74 years respectively [4.3]. The second, based on repeated cross-sectional surveys of population-representative households in England, found that among individuals who tested positive, 61% (95% credibility interval 53% to 69%) reported no symptoms, stably over time [4.4].

In a nationally representative prevalence survey of SARS-CoV-2 virus swab positivity in England (response rate 31%), during 1 May to 1 June 2020, the test-positive rate declined from 0.17% at age 25-34 years to 0.10% at age 55-64 [4.5]. Also, people with Asian (predominantly South Asian) ethnicity were more likely to be test positive than whites (adjusted OR 1.7, 0.86-2.5). Because of the low response rate, caution is needed in interpretation of these findings, but they highlight the potential for bias in risk estimates when mortality rates in the general population are used to estimate relative vulnerability. In particular, relatively lower exposure to infection at older ages could lead to underestimation of the vulnerability associated with increasing age. The study also found that among people who had tested positive, 69% (95%CI 61% to 76%) had been symptom-free for 7 days before the test.

A large population-based cohort study in Catalonia explored risk factors for being diagnosed with Covid-19, hospitalised with the disease, and for subsequent death among those diagnosed and hospitalised [4.6]. However, many of the people who died of Covid-19 had not been admitted to hospital, many of the hospitalised patients did not have an earlier out-patient diagnosis of Covid-19, and risks of mortality in relation to risk factors in the general population are not presented. Therefore, the findings cannot be used to estimate relative risks of vulnerability.

Four other reports, all from non-UK countries, assess relative risks of mortality among patients with diagnosed Covid-19 or hospitalisation for the disease [4.7 -4.10]. However, they cannot be used to estimate vulnerability in relation to risk factors because of uncertainties about the extent of bias from differential selection for testing or criteria for hospital admission.

An analysis of mortality by ethnicity in patients with a positive COVID-19 test in England from 1 March to 21 April, was limited to deaths in hospitals, and did not adjust for comorbidities [4.11].

UPDATE 5: 27 JULY 2020

In originally developing the Covid-age tool, we made an assumption that relative risks from different risk factors multiply, which we considered reasonable in the absence of persuasive evidence to the contrary (Section 3, paragraph 3). Since then, we have noted that an analysis of Scottish data by McKeigue and colleagues [3.1], found that that for most comorbidities, risk estimates were higher when analyses were restricted to participants aged < 60 years (Update 3). And in update 4, we reported new evidence from the OS study [4.1], indicating an important interaction of hypertension with age, with higher relative risk for hypertension in young adults than at older ages. This led us to add hypertension to our table of risk estimates, for the working age population.

We have now become aware of further indications that such interactions with age may apply to a number of other comorbidities. Quantitative data on this have not yet been published, but pending any such publication, we think it is worth highlighting that the vulnerability associated with some of the comorbidities in Table Z3 may be higher at young ages.

SECTION TWO: ASSESSMENT OF EVIDENCE ON SPECIFIC RISK FACTORS

A. Age

INITIAL ASSESSMENT: 20 MAY 2020

In the OS study, after adjustment for sex, multiple comorbidities, and various other risk factors, the risk of death from Covid-19 showed a near to exponential relationship to age among adults, such that the RR for a 10 year increase in age was approximately 2.5, and that for a single year of age 1.0945. Confidence intervals were not presented for the regression coefficient of log-transformed HR on age, but because the analysis was based on a large study sample (>17 million) and a large number of deaths (5,683), we would expect the estimated effect of age to be statistically precise, especially at ages 40-69 years.

Comparison with data from other sources

By way of comparison, Table A1 shows ONS data on mortality from Covid-19 (as an underlying cause of death) in England and Wales during March 2020 [2].

Table A1. Mortality from Covid-19 (deaths per 100,000) by sex and age, England and Wales, March 2020

Age band (years)	Male	Female
20-24	0.0	2.0
25-29	1.7	0.0
30-34	4.7	0.0
35-39	4.8	1.8
40-44	5.2	3.9
45-49	11.1	14.5
50-54	21.0	12.5
55-59	47.9	26.4
60-64	80.7	33.0
65-69	118.1	56.9

A 10-year increase in age from 50-54 to 60-64 was associated with a 3.8-fold increase in mortality in men and a 2.6-fold increase in women. For the increase in age from 55-59 to 65-69, the corresponding increases were 2.5 in men and 2.2 in women. When allowance is made for random sampling variation, and the fact that ONS data do not take account of covariates other than sex, these ratios seem compatible with those estimated from the OS study.

Conclusion

We conclude it is reasonable to assume that after allowance for other variables, risk of death from Covid-19 increases exponentially with age among people of working age, such that a one-year increase in age carries a relative risk of 1.0945.

Robustness of risk estimate

This estimate is derived from a large study and is compatible with data from an independent source. We consider it to be robust.

UPDATE 1: 26 MAY 2020

In the report by Barron et al [1.2], ORs for cumulative mortality from Covid-19 by age, adjusted for sex, ethnicity (where known), region, social deprivation and diabetes, were as in Table A2.

Table A2: Adjusted odds ratios for cumulative mortality from Covid-19 from the report by Barron et al.

Age (years)	OR	(95%CI)
40-49	0.11	(0.10-0.12)
50-59	0.35	(0.33-0.38)
60-69	1	
70-79	2.61	(2.50-2.74)

These imply a somewhat steeper increase in risk with age than in the OS study (ORs for 10 year increases 2.6 to 3.2). However, that may be, at least in part, because they are not adjusted for other comorbidities whose prevalence increases with age.

On balance, therefore, we do not think it is justified to change the adopted risk estimate for age at this stage. However, we have downgraded our confidence in the risk estimate to "moderately robust".

UPDATE 4: 16 JULY 2020

In the updated report from the OS study [4.1], the increase in risk with age among people of working age is a little steeper than in the earlier paper from which it evolved [1]. Thus, the relative risk for each additional 10 years of age was approximately 2.8. Given that this estimate is based on a larger sample of deaths than the earlier analysis, and is broadly consistent with other evidence that we have reviewed, including the study by Barron et al [1.2], we believe that it justifies a small change to our adopted risk estimate for age. We have therefore now adopted a relative risk of 1.1084 for each additional year of age. We judge this slightly amended risk estimate to be robust.

B. Sex

INITIAL ASSESSMENT: 20 MAY 2020

In the OS study, after adjustment for age, multiple comorbidities, and various other risk factors, the HR of death from Covid-19 in men relative to women was 1.99 (95%CI 1.88-2.10). We would not expect this risk estimate to be liable to any major bias.

Comparison with data from other sources

By way of comparison, in ONS statistics on mortality from Covid-19 (as the underlying cause of death) in England and Wales during March 2020 [2], the directly-standardised mortality rate per 100,000 was 97.5 in men and 46.6 in women, giving a ratio of 2.09. This ratio might change slightly if it were adjusted for comorbidities with differing prevalence by sex, but data from the Health Survey for England indicate that such differences in prevalence are generally small [4-7]. Thus, we consider that the ONS data, which relate to deaths outside as well as within hospital, support the relative risk from the OS study.

Conclusion

We conclude that after allowance for other risk factors, the relative risk of death from Covid-19 in men as compared with women should be taken as 2.0. Correspondingly, the risk in women relative to men can be taken as 0.5.

Robustness of risk estimate

Given the statistical precision of its source, and its close compatibility with other data, we judge this risk estimate to be robust.

UPDATE 1: 26 MAY 2020

In the new whole-population study by Barron et al, the OR for male vs. female sex after adjustment for age, ethnicity (where known), region, deprivation and diabetes, was 1.93 (95%CI 1.88-1.98) [1.2]. We consider this risk estimate to be compatible with, and supportive of, that which we previously adopted.

UPDATE 4: 16 JULY 2020

In the main analysis from the updated report of the OS study [4.1], the adjusted HR for male as compared with female sex (1.59, 95%CI 1.53-1.65) was substantially lower than that in the initial paper from which it evolved (1.99, 95%CI 1.88-2.10). This may be explained in part by expansion of the outcome measure to include deaths from Covid-19 outside hospital, such deaths being relatively more common among older women. However, it is of note that when analysis was censored at 6 April 2020, the risk estimate for male sex was significantly higher (HR 1.90, 95%CI 1.75-2.05). It is unclear what accounts for this difference, but it indicates that interpretation should be cautious. In response to the new evidence, we have reduced our adopted risk estimate for men relative to women to 1.8 (i.e. 0.6 for women relative to men), which is in line with the independent analysis of Scottish data by McKeigue et al [3.1]. In addition, we have downgraded the estimate to moderately robust.

C. Ethnicity

INITIAL ASSESSMENT: 20 MAY 2020

In the OS study, data on ethnicity were available for 74% of patients in the cohort. Table C1 shows HRs adjusted for sex, age, multiple comorbidities and various other risk factors, according to ethnicity and the date at which follow-up was censored.

Table C1. Adjusted hazard ratios for ethnic groups from the OS study according to date when follow-up was censored

Ethnic group		Follow-up to 25.4.20			Follow-up to 6.4.20	
		HR	(95%CI)		HR	(95%CI)
White		1			1	
Mixed		1.64	(1.19-2.26)		1.13	(0.62-2.05)
Asian or Asian British		1.62	(1.43-1.82)		1.77	(1.48-2.13)
Black		1.71	(1.44-2.02)		1.90	(1.48-2.45)
Other		1.33	(1.03-1.73)		1.81	(1.28-2.57)

Differences between corresponding risk estimates from the two analyses, especially for the less common ethnic groups (mixed, black and other) may have arisen through random sampling variation, and we have no reason to suspect that lower relative risks for some ethnic groups in the analysis with longer follow-up reflect a tendency for those groups to have avoided infection more effectively as the epidemic evolved. Thus, we consider that the risk estimates from the analysis with later censoring, which were statistically more precise, are the most reliable.

Comparison with data from other sources

The Office for National Statistics has published data on odds ratios for death related to Covid-19 in England and Wales during 2 March to 10 April 2020 according to ethnic group, with adjustment for age, geographical region, household composition, socioeconomic status and self-reported health at the 2011 census [8]. Table C2 shows risk estimates from that report for selected ethnic groups.

Table C2. Odds ratios for death related to Covid-19 according to ethnic group, England and Wales, 2 March to 10 April 2020

(Odds ratios are adjusted for age, geographical region, rural/urban, deprivation, household composition, socioeconomic status and self-reported health at the 2011 census).

Ethnic group		Male			Female	
		OR	(95%CI)		OR	(95%CI)
White		1			1	
Bangladeshi/Pakistani		1.81	(1.55-2.11)		1.61	(1.31-1.97)
Black		1.93	(1.70-2.18)		1.89	(1.63-2.20)
Indian		1.32	(1.15-1.53)		1.43	(1.20-1.71)

The estimated odds ratios for the Bangladeshi/Pakistani and Indian groups seem broadly compatible with the HR for the Asian or Asian British group in the OS study, as do the odds ratios for black men and women with the HR for the black group in the OS study.

Conclusion

We conclude that is reasonable to adopt relative risk estimates for ethnic group from the OS study as follows: Asian or Asian British 1.6; Black 1.7; Mixed 1.6; Other non-white 1.3. All of these risk estimates are relative to white as the reference.

Robustness of risk estimate

The risk estimate for the Asian or Asian British group is fairly precise statistically, and accords with independent ONS data. We therefore judge it to be moderately robust. The other risk estimates are less precise and we regard them as provisional.

UPDATE 1: 26 MAY 2020

In the new whole population study by Barron et al, ORs for death in hospital from Covid-19, adjusted for age, sex, region, social deprivation and diabetes, and relative to white ethnic group, were 1.36 (95%CI 1.29-1.44) for Asian, 1.73 (95%CI 1.63-1.83) for black, and 1.43 (95%CI 1.23-1.67) for mixed [1.2]. These results are consistent with our adopted risk estimates for black and mixed ethnicity, but the OR for Asian ethnicity suggests a lower relative risk than that which we previously adopted (1.6). The difference may in part reflect less extensive adjustment for comorbidities in the new study, but it is an indication that the chosen value may be slightly too high.

In the light of this new evidence, we have slightly reduced the adopted relative risk for Asian ethnicity to 1.5, and upgraded the robustness of that for black ethnicity to moderately robust.

UPDATE 3: 29 JUNE 2020

A new analysis of data from the ISARIC cohort assessed outcomes among 30,693 patients with recorded (self-reported) ethnicity, who were admitted to British hospitals during 6 February to 8 May 2020, and followed to 22 May [3.2]. After adjustment for age, sex and location, HRs for fatality relative to white ethnicity were 1.19 (95%CI 1.05-1.36) for those of South Asian origin, 1.05 (95%CI 0.91-1.26) for black ethnicity, and 0.99 (95%CI 0.89-1.10) for other ethnic minorities. There was no interaction of ethnicity with sex or age. The higher risk in the South Asian group was in part explained by a higher prevalence of diabetes. Given that these risk estimates are derived from patients who had been admitted to hospital, and that ethnicity may also be associated with higher rates of hospitalisation in those contracting Covid-19, we do not think that they indicate any need to revise our currently adopted, somewhat higher, risk estimates for case-fatality by ethnicity.

A second paper, with the same first two authors, reports a similar analysis for 23,577 Covid-19 patients admitted to UK hospitals up to 25 April 2020 [3.3]. The findings on ethnicity are broadly similar, but it is unclear to what extent they are subsumed by the later report.

An analysis of risk factors for hospital admission with Covid-19 in the Biobank cohort found an increased risk for black (OR 2.66, 95%CI 1.82-3.91) and Asian (OR 1.43, 95%CI 0.91-2.26) as compared with white ethnicity [3.4]. However, these risk estimates, while adjusted for various other factors, do not allow for region, which may have been an important determinant of exposure to infection.

Overall, we do not think that the newly reported findings that we have reviewed give us reason to revise our adopted risk estimates for ethnicity.

UPDATE 4: 16 JULY 2020

In the newly reported results from the OS study, risk estimates for some ethnic groups are a little lower than in earlier analyses, and findings are presented for more detailed categories of ethnicity [4.1]. There is a suggestion that people of Bangladeshi origin may be more vulnerable than those of Indian or Pakistani origin, but confidence intervals are fairly wide, and we do not think the evidence is yet sufficiently strong to adopt separate risk estimates for these three ethnic groups in our model. However, in response to the new information, we have reduced our adopted relative risk estimate for mixed race to 1.4, keeping it as provisional.

D. Obesity

INITIAL ASSESSMENT: 20 MAY 2020

In the OS dataset, body mass index (BMI) was ascertained from measurements of weight in the past 10 years, when individuals were >16 years old, and was available for 78% of the cohort.

Table D1 shows HRs, adjusted for sex, age, multiple comorbidities and various other risk factors, according to levels of BMI.

Table D1. Adjusted hazard ratios for categories of body mass index from OS study according to date when follow-up was censored

BMI (Kg/m^2)		Censored at 25.4.20			Censored at 6.4.20	
		HR	(95%CI)		HR	(95%CI)
<30		1			1	
30-34.9		1.27	(1.18-1.36)		1.39	(1.25-1.54)
35-39.9		1.56	(1.41-1.73)		1.62	(1.39-1.90)
≥40		2.27	(1.99-2.58)		2.45	(2.00-3.01)

It is possible that the lower HRs with longer follow-up reflect selective shielding of people with obesity as the epidemic evolved, and for this reason, we consider that the analysis censored at 6 April provides the more reliable estimate of RR for our risk model.

Comparison with data from other sources

In the ISARIC cohort, of patients admitted to British hospitals with Covid-19, obesity "as recognised on admission by clinical staff" (not sub-divided by severity) had an adjusted HR of 1.37 (95%CI 1.16-1.63) for death in hospital. However, the prevalence of obesity in the ISARIC cohort was remarkably low (approximately 9%, as compared with prevalence rates from the 2017 Health Survey for England by sex and 10-year age band in the order of 30% [5]), suggesting serious under-ascertainment.

Conclusion

We consider that the apparently low prevalence of obesity among hospitalised Covid-19 patients in the ISARIC cohort is almost certainly an artefact of incomplete ascertainment, and we therefore accepted the risk estimates from the OS study (shorter follow-up period) for inclusion in our risk model, as set out in Table D2.

Table D2. Adopted relative risk estimates for obesity

BMI (Kg/m^2)	Relative risk
<30	1
30-34.9	1.4
35-39.9	1.6
≥40	2.4

Robustness of risk estimates

These risk estimates are derived from a single, large and nationally representative study, but with limited support from other investigations. We therefore consider them provisional.

UPDATE 1: 26 MAY 2020

In the large cohort study of diabetes patients by Holman et al [1.3], after adjustment for age, sex, ethnicity, region, social deprivation, HbA1c level, time since diagnosis of diabetes, eGFR, smoking, previous stroke and previous heart failure, HRs for death related to Covid-19 varied with BMI as shown in Table D3.

Table D3. Adjusted hazard ratios for death associated with Covid-19 by body mass index

Body mass index (Kg/m^2)	Type 1 diabetes		Type 2 diabetes	
	HR	(95%CI)	HR	(95%CI)
<20	2.11	(1.32-3.38)	2.26	(2.04-2.5)
20-24.9	1.38	(1.04-1.83))	1.31	(1.23-1.39)
25-29.9	1		1	
30-34.9	1.5	(1.13-1.99)	1.04	(0.98-1.11)
35-39.9	1.7	(1.18-2.46)	1.16	(1.08-1.26)
≥40	2.15	(1.37-3.36)	1.64	(1.5-1.79)
Missing	1.8	(1.23-2.63)	1.86	(1.73-2.01)

The risk estimates among patients with Type 1 diabetes, although they relate to a different reference (BMI 25-29.9), are broadly consistent with those that were adopted for obesity in our risk model. However, those in patients with Type 2 diabetes are lower, suggesting either that the combined effects of Type 2 diabetes and obesity on relative risk are less than multiplicative, or that our adopted risk estimates obesity are a little too high.

At this stage, we have not changed the risk estimates for obesity, but the possibility of a non-multiplicative interaction with Type 2 diabetes, or that they overestimate risk, reinforces our view that they should be classed only as provisional.

UPDATE 4: 16 JULY 2020

In the updated analysis from the OS cohort, the HR for BMI 30 to 34-9 Kg/m^2 is a little lower, being 1.30 rather than 1.39 with censoring of follow-up at 6.4.20, and even lower in the analysis with full follow-up [4.1]. In response, we have reduced our adopted estimate of relative risk from 1.4 to 1.3. The new data do not indicate a need to change the adopted risk estimates for more severe categories of obesity.

E. Asthma

INITIAL ASSESSMENT: 20 MAY 2020

In the OS study, asthma was sub-classified according to whether or not it had been treated with oral corticosteroids in the year before baseline (severe or mild). Table E1 shows the prevalence of these categories of asthma in the study cohort, and the associated hazard ratios for death from Covid-19, after adjustment for sex, age, multiple comorbidities and various other risk factors.

Table E1. Prevalence of asthma in OS cohort, and adjusted HRs for death from Covid-19 according to date when follow-up was censored

Severity of asthma		Prevalence (%) in cohort		Censored at 25.4.20			Censored at 6.4.20	
				HR	(95%CI)		HR	(95%CI)
No asthma		84.1		1			1	
Mild asthma		14.2		1.11	(1.02-1.20)		1.14	(1.01-1.29)
Severe asthma		1.7		1.25	(1.08-1.44)		1.39	(1.12-1.73)

It is possible that, as the epidemic evolved, patients with more severe asthma took more extreme measures to reduce their risk of contracting Covid-19, leading to a lower HR in the analysis over the longer follow-up period. Thus the HR from the analysis with shorter follow-up may be more reliable.

Comparison with data from other sources

In the ISARIC cohort of hospitalised patients, the overall prevalence of asthma (not sub-divided by severity) was 14%, which is similar to that in the OS cohort (15.9%). Moreover, prevalence rates for doctor-diagnosed asthma in the 2018 Health Survey for England were even higher [4]. The report from the ISARIC study does not present a risk estimate for death in patients with asthma, although it does for other comorbidities with clearly increased risk.

Conclusion

When viewed together, the above findings indicate that most asthma is associated with little, if any, increase in risk of mortality from Covid-19. However, a small elevation of risk seems likely in people with more severe asthma that has required use of oral corticosteroids in the past year. We therefore adopted relative risk estimates for our risk model as set out in Table E2.

Table E2. Adopted relative risk estimates for asthma

Severity of asthma	Relative risk
None	1
Mild (no requirement for oral corticosteroids in past year)	1.1
Severe (requiring oral corticosteroids in past year)	1.4

Robustness of risk estimate

Although derived from a single study, these risk estimates appear compatible with other independent data, and we regard them as moderately robust

UPDATE 3: 29 JUNE 2020

In a new analysis from the OS collaborative, based on 817,973 patients with asthma, in comparison with those using only a short-acting beta agonist, risk was elevated for use of high-dose inhaled corticosteroids (HR 1.52, 95%CI 1.08-2.14), but showed no clear relation to low/medium dose inhaled corticosteroids (HR 1.10, 95%CI 0.82-1.49) [3.5]. However, the analysis did not consider concomitant use of oral corticosteroids, and therefore we do not think that it can be used to refine our adjusted risk estimates for asthma.

F. Diabetes

INITIAL ASSESSMENT: 20 MAY 2020

In the OS study, diabetes was classified to three mutually exclusive categories, according to whether an HbA1c measurement had been made in the last 15 months, and if so, whether the level was <58 mmol/mol (controlled diabetes) or higher (uncontrolled diabetes). Table F1 shows the prevalence of these categories of diabetes in the OS cohort, and their HRs for death from Covid-19 during follow-up.

Table F1. Prevalence of diabetes in the OS cohort, and adjusted HRs for death from Covid-19 according to date when follow-up was censored

Severity of diabetes		Prevalence (%) in cohort		Censored at 25.4.20			Censored at 6.4.20	
				HR	(95%CI)		HR	(95%CI)
No diabetes		90.9		1			1	
Controlled		6.0		1.50	(1.40-1.60)		1.48	(1.33-1.65)
Uncontrolled		2.8		2.36	(2.18-2.56)		2.57	(2.27-2.91)
No recent HbA1c measure		1.1		1.87	(1.63-2.19)		1.68	(1.33-2.12)

There was no clear indication that HRs with longer follow-up were lowered as a consequence of selective shielding by diabetic patients. Therefore, the statistically more robust HRs from the longer follow-up period were judged to be the more reliable.

Comparison with data from other sources

To check on the plausibility of the risk estimates from the OS study, we analysed data on diabetes from the ISARIC study and the 2017 Health Survey for England [5]. Table F2 shows approximate numbers of patients by sex and age in the ISARIC cohort (estimated by measuring the lengths of bars in a bar chart), the prevalence of doctor-diagnosed diabetes in the same age and sex strata in the 2017 Health Survey for England, and calculations from these data of the numbers of patients with doctor-diagnosed diabetes that might have been expected in the ISARIC cohort if diabetes had no effect on hospital admission for Covid-19. Summation of expected numbers across all of the strata indicates that the overall expected percentage prevalence of doctor-diagnosed diabetes in the ISARIC cohort would be: 100*(586+302)/(4401+2807) = 12%.

In contrast, the reported prevalence of uncomplicated diabetes in the ISARIC cohort was 19%, suggesting a relative risk for hospital admission in the order of 19/12 = 1.6.

This calculation has many limitations. Unlike the ISARIC study, the Heath Survey for England did not cover Wales or Scotland, and its case definition and method of ascertaining diabetes differed from that in the ISARIC study. Furthermore, the calculated ratio takes no account of possibly higher fatality among Covid-19 patients with diabetes once they are admitted to hospital. When these weaknesses are taken into account, the calculated ratio seems compatible with the risk estimates from the OS study, and gives them added plausibility.

Table F2. Calculation of expected numbers of patients with doctor-diagnosed diabetes in ISARIC cohort, based on prevalence in the 2017 Health Survey for England

Entries in the table are rounded to the nearest whole number, but calculations have used original unrounded numbers. Therefore numbers as presented may not sum exactly to reported totals.

Aggregated age band (years)	Approximate numbers in ISARIC cohort			Prevalence % of DDD* in 2017 Health Survey for England		Expected numbers of cases in ISARIC cohort	
	Male	Female		Male	Female	Male	Female
0-14	73	36					
16-24	36	40		1	0	0	0
25-34	84	124		1	0	1	0
35-44	233	131		3	2	8	3
45-54	459	339		9	5	42	18
55-64	674	357		11	7	72	26
65-74	901	474		19	11	170	52
75+	1940	1305		15	16	292	204
Total	4401	2807				586	302

*Doctor-diagnosed diabetes

Conclusions

We concluded that it is reasonable to adopt risk estimates for diabetes from the OS study for our risk model as set out in Table F3.

Table F3. Adopted relative risks for diabetes

Severity of diabetes	Relative risk
No diabetes	1
Controlled	1.5
Uncontrolled	2.4
No recent HbA1c measure	1.9

Robustness of risk estimates

In view of their derivation from a large and nationally representative dataset, and their consistency with data from other sources, we consider these risk estimates to be moderately robust.

UPDATE 1: 26 MAY 2020

The new study reported by Barron et al [1.2] found that in comparison with no diabetes, and after adjustment for age, sex, ethnicity (where available), region, and social deprivation, ORs for death in hospital from Covid-19 were 3.50 (95%CI 3.15-3.88) for Type 1 diabetes, 2.01 (95%CI 1.96-2.07) for Type 2 diabetes, and 2.16 (1.70-2.74) for other diabetes. With adjustment also for coronary heart disease, cerebrovascular disease and heart failure, these risk estimates reduced slightly to 2.86 for Type 1 diabetes and 1.81 for Type 2 diabetes.

Furthermore, in cohorts of almost all patients in England with Type 1 or Type 2 diabetes, after adjustment for age, sex, ethnicity, region, social deprivation, time since diagnosis of diabetes, eGFR, BMI, smoking, previous stroke and previous heart failure, HRs for death related to Covid-19 by level of diabetic control, were as shown in Table F4 [1.3].

Table F4 Adjusted hazard ratios for death associated with Covid-19 in patients with Type 1 and Type 2 diabetes according to level of diabetic control

HbA1c (mmol/mol)	Type 1 diabetes			Type 2 diabetes		
	Prevalence (%)	HR	(95%CI)	Prevalence (%)	HR	(95%CI)
45-48	6.8	1,22	(0.78-1.91)	25.1	1.11	(1.04-1.18)
49-53	8.2	1		20.6	1	
54-58	9.5	0.73	(0.44-1.20)	12.7	1.05	(0.97-1.13)
59-74	29.3	1.15	(0.79-1.67)	19.2	1.23	(1.15-1.32)
75-85	11.4	1.31	(0.85-2.03)	5.5	1.37	(1.24-1.51)
≥86	11.8	2.19	(1.46-3.29)	6.1	1.62	(1.48-1.79)
Missing	23.0	1.60	(1.05-2.43)	10.9	1.57	(1.46-1.70)

By combining the data in Table F4 with the adjusted overall HRs of 2.86 and 1.81 for Type 1 and Type 2 diabetes respectively, it is possible to derive approximate estimates of risk relative to no diabetes for subcategories of diabetes specified by type and level of control. Suppose, for example, that relative to no diabetes, the risk for Type 1 diabetes with HbA1c of 49-53 mmol/mol is R. Corresponding relative risks for the other strata of HbA1c can be calculated as the product of R and their HR in Table F4. It is then possible to calculate the overall relative risk for Type 1 diabetes as a function of R, by deriving an average of the stratum-specific relative risks, weighted according to their prevalence in the cohort. This should equate approximately to the measured overall HR of 2.86 for Type 1 diabetes, allowing calculation of R, and thereby of the relative risk for each of the other strata. The calculation is shown for Type 1 diabetes in Table F5, and for Type 2 diabetes in Table F6.

Table F5. Calculation of risks relative to no diabetes for sub-categories of Type 1 diabetes defined by level of HbA1c

HbA1c (mmol/mol)	Risk relative to no diabetes	Prevalence (%) in cohort	Product of relative risk and prevalence	Risk relative to no diabetes calculated by substituting 2.86/1.35 for R
45-48	1,22*R	6.8	8.30*R	2.6
49-53	R	8.2	8.20*R	2.1
54-58	0.73*R	9.5	6.94*R	1.5
59-74	1.15*R	29.3	33.70*R	2.4
75-85	1.31*R	11.4	14.93*R	2.8
≥86	2.19*R	11.8	25.84*R	4.6
Missing	1.60*R	23.0	36.80*R	3.4
Total			134.71*R	
Weighted average			1.35*R	

Table F6. Calculation of risks relative to no diabetes for sub-categories of Type 2 diabetes defined by level of HbA1c

HbA1c (mmol/mol)	Risk relative to no diabetes	Prevalence (%) in cohort	Product of relative risk and prevalence	Risk relative to no diabetes calculated by substituting 1.81/1.20 for R
45-48	1.11*R	25.1	27.86*R	1.7
49-53	R	20.6	20.60*R	1.5
54-58	1.05*R	12.7	13.34*R	1.6
59-74	1.23*R	19.2	23.62*R	1.9
75-85	1.37*R	5.5	7.54*R	2.1
≥86	1.62*R	6.1	9.88*R	2.4
Missing	1.57*R	10.9	17.11*R	2.4
Total			119.95*R	
Weighted average			1.20*R	

Given that Type 2 diabetes accounted for more than 90% of all diabetes in the national population, these risk estimates, seem broadly compatible with our previously adopted risk estimates of 1.5, 2.4 and 1.9 respectively for diabetes with HbA1c <58 mmol/mol, ≥58 mmol/mol and missing. However, the new data indicate a substantially higher risk in association with Type 1 diabetes, and we have therefore decided to revise our adopted relative risk estimates as indicated in Table F7. We recognise that these risk estimates are approximations, and that is why we have not attempted to distinguish too finely between levels of control. Also, we have taken into account that the overall ORs for types of diabetes in the study by Barron et al [1.2] were not adjusted for BMI or chronic kidney disease. From

the evidence in the Barron study, it seems reasonable to classify other diabetes (including maturity onset diabetes of the young) with Type 2 diabetes.

Table F7. New adopted relative risk estimates for diabetes.

Type of diabetes	Most recent HbA1c (mmol/mol)	Relative risk
Type 1	≤58	2.0
	>58	2.7
	Unknown	3.3
Type 2 and other	≤58	1.5
	>58	2.0
	Unknown	2.3

In view of their compatibility with the OS study, we class these risk estimates as moderately robust

G. Cardiovascular disease

INITIAL ASSESSMENT: 20 MAY 2020

In the OS study, chronic heart disease (CHD) included heart failure, ischaemic heart disease, and severe valve or congenital heart disease likely to require lifelong follow-up. Among the 6.7% of cohort members with CHD, the HR for death from Covid-19, adjusted for sex, age, multiple comorbidities and various other risk factors was 1.27 (95%CI 1.20-1.35) when follow-up was censored at 25.4.20, and 1.33 (95%CI 1.22-1.46) when it was censored at 6.4.20.

Comparison with data from other sources

No directly comparable data are available for other studies in the UK, but in the ISARIC study, the prevalence of CHD among Covid-19 patients admitted to hospitals in England Wales and Scotland was 29%, with an adjusted HR for death of 1.31 (95%CI 1.18-1.45). Unless people with CHD who contract Covid-19 have no increased risk of being admitted to hospital, which seems unlikely, this would suggest a relative risk for mortality among all Covid-19 cases in the wider community of at least 1.3.

Conclusions

Although based on a large and nationally representative dataset, the OS risk estimates for CHD seem low in comparison with what might be expected from the ISARIC study. Furthermore, the HR in models with censoring at 25.4.20 reduced substantially (from 2.01 to 1.27) when adjusted for other risk factors in addition to sex and age. It is unclear which factors of adjustment contributed most to such a large reduction in the risk estimate.

With these considerations in mind, we tentatively adopted a relative risk of 1.4 for CHD in our risk model.

Robustness of risk estimate

The relative risk for CHD seems likely to be higher than 1.4, but how much higher is currently quite uncertain. The value adopted for the risk model should therefore be classed as provisional.

UPDATE 1: 26 MAY 2020

In the updated report on the ISARIC study [1.1], the adjusted HR for death in hospitalised Covid-19 patients with CHD was lower than previously reported at 1.16 (95%CI 1.08-1.24).

In the large population-based cohort study by Barron et al [1.2], after adjustment for age, sex, ethnicity, region, social deprivation, and diabetes (classified by type), ORs for cumulative mortality from Covid-19 were 1.32 (95%CI 1.28-1.36) for coronary heart disease, 2.23 (95%CI 2.16-2.31) for cerebrovascular disease, and 2.23 (95%CI 2.14-2.31) for heart failure. Putting these results alongside those from the OS study, we think it is reasonable to adopt refined relative risk estimates for cardiovascular disease as set out in Table G1:

Table G1. Revised relative risk estimates adopted for cardiovascular disease

Comorbidity	Adopted relative risk
Heart failure	2.2
Other chronic heart disease	1.3
Cerebrovascular disease	2.2

As these risk estimates come largely from a single, albeit large, cohort study, without adjustment for the full range of other potentially relevant comorbidities, we class them as provisional.

UPDATE 4: 16 JULY 2020

The updated report from the OS study includes important new information on risks associated with hypertension (defined as diagnosed hypertension, or the most recent recording indicating systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) [4.1]. Although hypertension was not associated with increased mortality when results were averaged across the whole study sample, there was a strong interaction with age, with elevated HRs at younger ages, and low HRs at older ages (Table G2).

Table G2 Hazard ratios for hypertension by age in the OpenSAFELY study [4.1]

Age band (years)	HR	(95%CI)
18 to <40	3.11	(1.68-5.71)
40 to <50	2.75	(1.97-3.83)
50 to <60	2.07	(1.73-2.47)
60 to <70	1.32	(1.17-1.50)
70 to <80	0.94	(0.86-1.02)
≥80	0.73	(0.69-0.78)

Across the range of working ages, this pattern of risk can be modelled approximately by assuming a linear decline in HR with age, and applying the equation HR = 0.94 + {(75 – age)*(3.11 – 0.94)/45}. Table G3 shows the estimated HRs (rounded to one decimal place) that are derived, and it can be seen that the values for the mid-points of the age categories in Table G2 agree reasonably well with the reported risk estimates for those age categories.

Table G3 Modelled hazard ratios by age

Age (years)	Modelled HR
20	3.6
21-22	3.5
23-25	3.4
26-27	3.3
28-29	3.2
30-31	3.1
32-33	3.0
34-35	2.9
36-37	2.8
38-39	2.7
40-41	2.6
42-43	2.5
44-45	2.4
46-47	2.3
48-49	2.2
50-51	2.1
52-54	2.0
55-56	1.9
57-58	1.8
59-60	1.7
61-62	1.6
63-64	1.5
65-66	1.4
67-68	1.3
69-70	1.2
71-72	1.1
73	1.0

These estimates for risk associated with hypertension at working ages are based on a large and representative study sample, and we have therefore adopted them provisionally in our risk model.

H. Chronic respiratory disease other than asthma

INITIAL ASSESSMENT: 20 MAY 2020

In the OS study, this category of comorbidity included chronic obstructive pulmonary disease (COPD), fibrosing lung disease, bronchiectasis and cystic fibrosis. After adjustment for sex, age, multiple comorbidities and various other risk factors, it carried HRs of 1.78 (95%CI 1.67-1.90) when follow-up was censored at 25.4.20, and 1.97 (95%CI 1.77-2.18) with censoring at 6.4.20. The lower HR after longer follow-up may in part reflect selective shielding of people with chronic respiratory disease as the epidemic evolved.

Comparison with data from other sources

In the ISARIC study of patients admitted to hospital with Covid-19 in England, Wales and Scotland, chronic pulmonary disease other than asthma was reported in approximately 17% of cohort members, and carried an adjusted HR for death of 1.19. Table H1 shows approximate numbers of patients by sex and age in the ISARIC cohort (estimated by measuring the lengths of bars in a bar chart), the prevalence of doctor-diagnosed COPD (including chronic bronchitis and emphysema) in the same age and sex strata in the 2010 Health Survey for England [7], and calculations from these data of the numbers of patients with doctor-diagnosed COPD that might have been expected in the ISARIC cohort if COPD had no effect on hospital admission for Covid-19, and its prevalence in the general population was at similar levels in 2020. Summation across all of the strata indicates that the overall expected percentage prevalence of doctor-diagnosed COPD in the ISARIC cohort would be: 100*(339+205)/(4401+2807) = 8%. In addition, a smaller prevalence of other types of chronic pulmonary disease might be expected. When the 17% observed prevalence of chronic pulmonary disease is set alongside findings from this rough analysis of expected numbers, and also the HR of 1.2 for death in patients with chronic pulmonary disease, the OS relative risk estimates look highly plausible.

Table H1. Calculation of expected numbers of patients with doctor-diagnosed COPD in ISARIC cohort, based on prevalence in the 2010 Health Survey for England

Aggregated age band (years)	Approximate numbers in ISARIC cohort			Prevalence % of DDCOPD* in 2010 Health Survey for England		Expected numbers of cases in ISARIC cohort	
	Male	Female		Male	Female	Male	Female
0-14	73	36					
16-24	36	40		1	0	0	0
25-34	84	124		2	2	2	2
35-44	233	131		2	4	5	5
45-54	459	339		4	5	18	17
55-64	674	357		6	8	40	29
65-74	901	474		11	10	99	47
75+	1940	1305		9	8	175	104
Total	4401	2807				339	205

*Doctor-diagnosed COPD

Conclusions

Based on these considerations, we assigned a relative risk of 1.9 to chronic respiratory disease other than asthma.

Robustness of risk estimate

The adopted relative risk estimate is derived from a large and nationally representative cohort, and supported by data from an independent source. We consider it to be moderately robust.

UPDATE 1: 26 MAY 2020

In the updated report of the ISARIC study, there was no major change in the adjusted HR for death from Covid-19 in relation to chronic pulmonary disease (updated value = 1.17) [1.1].

UPDATE 3: 29 JUNE 2020

A new analysis from the OS collaborative, which focused on 148,588 patients with COPD, found that after adjustment for sex, age and multiple comorbidities, risk of Covid-19-related death was modestly elevated in relation to use of inhaled corticosteroids as compared with use of a long-acting beta-agonist or muscarinic antagonist (HR 1.38, 95%CI 1.08-1.75) [3.5]. However, the report did not provide information on the overall relative risk of death among people with COPD, and did not consider use of oral corticosteroids. For these reasons, we do not think that it can be used to modify our currently adopted risk estimates for chronic respiratory disease.

I. Chronic kidney disease

INITIAL ASSESSMENT: 20 MAY 2020

In the OS study, chronic kidney disease (CKD) was defined as a glomerular filtration rate <60mL/min/1.73m^2, as estimated from the most recent serum creatinine measurement, where available. It was present in 6.3% of cohort members. In analyses that adjusted for sex, age, multiple comorbidities and various other risk factors, it carried HRs for mortality from Covid-19 of 1.72 (95%CI 1.62-1.83) when follow-up continued to 25.4.20, and 1.75 (95%CI 1.58-1.92) when it was censored at 6.4.20. There was no indication of any major attenuation of risk with longer follow-up because of selective shielding of patients with CKD.

Comparison with data from other studies

In the ISARIC cohort of patients hospitalised with Covid-19, the reported prevalence of CKD was approximately 14%, and it carried an adjusted HR of 1.25 for death. Table I1 shows approximate numbers of patients by sex and age in the ISARIC cohort (estimated by measuring the lengths of bars in a bar chart), the prevalence of doctor-diagnosed CKD in the same age and sex strata in the 2016 Health Survey for England [6], and calculations from these data of the numbers of patients with doctor-diagnosed CKD that might have been expected in the ISARIC cohort if CKD had no effect on hospital admission for Covid-19. Summation across all of the strata indicates that the overall expected percentage prevalence of doctor-diagnosed CKD in the ISARIC cohort would be: 100*(185+89)/(4401+2807) = 4%. This implies a ratio of observed to expected prevalence of 14%/4% = 3.5. It is possible, however, that doctor-diagnosed CKD, which after allowance for sex and age, had a lower prevalence in the 2016 Health Survey for England than CKD as determined in the OS study, represented a more severe spectrum of disease. When this is taken into account, the findings from this further analysis of ISARIC data do not call into question the relative risk estimates from the OS study.

Table I1. Calculation of expected numbers of patients with doctor-diagnosed CKD in ISARIC cohort, based on prevalence in the 2016 Health Survey for England

Entries in the table are rounded to the nearest whole number, but calculations have used original unrounded numbers. Therefore numbers as presented may not sum exactly to reported totals.

Aggregated age band (years)	Approximate numbers in ISARIC cohort			Prevalence % of DDCKD* in 2016 Health Survey for England		Expected numbers of cases in ISARIC cohort	
	Male	Female		Male	Female	Male	Female
0-14	73	36					
16-24	36	40		0	1	0	0
25-34	84	124		1	1	1	1
35-44	233	131		1	1	3	1
45-54	459	339		2	2	9	5
55-64	674	357		4	2	24	6
65-74	901	474		5	3	44	16
75+	1940	1305		5	5	104	60
Total	4401	2807				185	89

*Doctor-diagnosed CKD

Conclusions

Based on the above considerations, we adopted a relative risk of 1.7 for CKD defined as a glomerular filtration rate <60mL/min/1.73m^2, as estimated from the most recent serum creatinine measurement.

Robustness of risk estimate

This risk estimate is based on findings in a large and nationally representative cohort, and is broadly consistent with independent data from other sources. As such, we judge it to be moderately robust.

UPDATE 1: 26 MAY 2020

The large cohort study of patients with diabetes by Holman et al [1.3] provides estimated HRs for death related to Covid-19 by level of eGFR. Results were presented separately for people with Type I and Type 2 diabetes, with adjustment for age, sex, ethnicity, social deprivation, region, most recent HbA1c, time since diagnosis of diabetes, BMI, smoking, previous stroke and previous heart failure (Table I2).

Table I2. Adjusted hazard ratios for death related to Covid-19 in diabetic patients according to estimated glomerular filtration rate

Estimated glomerular filtration rate (mL/min/1.73m^2)	Type 1 diabetes		Type 2 diabetes	
	HR	(95%CI)	HR	(95%CI)
≥60	1		1	
45-59	1.92	(1.46-2.53)	1.37	(1.30-1.45)
30-44	2.16	(1.59-2.93)	1.75	(1.64-1.86)
15-29	2.98	(2.04-4.35)	2.24	(2.04-2.45)
<15	6.85	(4.65-10.09)	4.83	(4.28-5.46)
Missing	1.45	(0.83-2.55)	0.82	(0.70-0.97)

The large majority of patients with eGFR <60 mL/min/1.73m^2 had values in the range from 30 to 59, for which the HRs for Covid-19-related death ranged from 1.37 to 2.16. When compared with our previously adopted relative risk of 1.7 for CKD in the general population, these results do not suggest any major departure from multiplication of relative risks when diabetes and CKD are present in combination.

UPDATE 4: 16 JULY 2020

The updated analysis from the OS study [4.1] provides separate risk estimates for two levels of kidney function. When follow-up was censored at 6.4.20, HRs were 1.49 (95%CI 1.36-1.63) for an eGFR of 30-60 mL/min and 2.98 (95%CI 2.57-3.46) for an eGFR of <30 mL/min. With full follow-up, both HRs were lower (1.33 and 2.52 respectively), possibly reflecting an effect of selective shielding. A secondary analysis suggested a particularly high risk associated with a history of dialysis or end-stage renal failure (HR 3.69, 95%CI 3.10-4.39). It is unclear what proportion of those with eGFR <30 mL/min fell into this category, but it is likely to have been small.

Given that this gradient of risk is compatible with findings in diabetic patients (Table I2), we think the estimates can be used to refine the assessment of risk for chronic kidney disease.

We have therefore revised our adopted relative risk estimates for CKD as set out in Table I3.

Table I3 Revised relative risk estimates adopted for chronic kidney disease

Category of chronic kidney disease	Adopted relative risk
Estimated GFR 30-60 mL/min	1.5
Estimated GFR < 30 mL/min	3.0
History of dialysis or end-stage renal failure	3.7

As before, we consider the estimates for CKD to be moderately robust.

X. Risk factors not included in risk model

INITIAL ASSESSMENT: 20 MAY 2020

Two potential determinants of vulnerability carried no apparent increase in the risk of death from Covid-19 in the OS study, after account had been taken of sex, age and comorbidities. These were smoking and hypertension. Adjusted HRs with follow-up to 25.4.20 were 0.88 (95%CI 0.79-0.99) for current vs. never smokers, and 0.95 (95% CI 0.89-1.01) for high blood pressure or diagnosed hypertension.

These risk factors were therefore excluded from the risk model.

UPDATE 1: 26 MAY 2020

In the large cohort study of patients with diabetes by Holman and colleagues [1.3], after adjustment for age, sex, ethnicity, social deprivation, region, HbA1c, eGFR, BMI, previous stroke and previous heart failure (but not for asthma or other respiratory disease), HRs for current smokers relative to never smokers were <1, both in people with Type 1 and Type 2 disease. Moreover, HRs in ex-smokers were barely elevated (1.10 and 1.12). Also, there was reported to be no statistically significant increase in risk in association with having been prescribed anti-hypertensive drugs. These new data support the decision not to include smoking or hypertension in our risk model.

UPDATE 2: 14 JUNE 2020

Further studies reported since the last update support the assessment that after account is taken of other risk factors, any vulnerability from smoking [2.2] or hypertension is small [2.1-2.3]. However, this does not preclude the possibility of a larger elevation of risk in association with some, as yet unidentified, sub-categories of hypertension.

UPDATE 4: 16 JULY 2020

The updated report from the OS study [4.1] indicates that although there was no overall elevation of risk for hypertension, there was an important interaction between hypertension and age, with increased risks at younger ages. In response to this observation, we have now added hypertension to our risk model (see Section G).

Y. Rarer comorbidities

INITIAL ASSESSMENT: 20 MAY 2020

The OS study also provides adjusted risk estimates for a number of other rarer comorbidities, for which we have not as yet identified any independent corroborating data. HRs for these comorbidities, adjusted for sex, age, multiple other comorbidities and various other risk factors are summarised in Table Y1, together with the relative risks that we have carried forward to our risk model. The choice of the values taken forward weighed the greater statistical precision of the estimates based on longer follow-up against the possibility that they may in some cases have been biased downwards because of selective shielding by people with the comorbidity. All adopted values are considered provisional.

Table Y1. Adjusted hazard ratios for other comorbidities from the OS cohort, and relative risk estimates taken forward to risk model

Comorbidity	Follow-up censored at 25.4.20		Follow-up censored at 6.4.20		RR adopted for risk model
	HR	(95%CI)	HR	(95%CI)	
Non-haematological cancer					
None	1		1		
Diagnosed <1 year ago	1.56	(1.29-1.89)	1.51	(1.10-2.05)	1.6
Diagnosed 1-4.9 years ago	1.19	(1.04-1.35)	1.36	(1.13-1.65)	1.2
Diagnosed ≥5 years ago	0.97	(0.88-1.06)	0.92	(0.79-1.06)	1.0
Haematological malignancy					
None	1		1		
Diagnosed <1 year ago	3.52	(2.41-5.14)	2.60	(1.30-5.22)	3.5
Diagnosed 1-4.9 years ago	3.12	(2.50-3.89)	3.67	(2.66-5.06)	3.1
Diagnosed ≥5 years ago	1.88	(1.55-2.29)	1.64	(1.18-2.28)	1.9
Liver disease	1.61	(1.33-1.95)	1.86	(1.40-2.47)	1.6
Chronic neurological disease other than stroke or dementia*	2.46	(2.19-2.76)	2.28	(1.88-2.76)	2.5
Organ transplant	4.27	(3.20-5.70)	2.62	(1.51-4.57)	4.3
Spleen diseases†	1.41	(0.93-2.12)	1.87	(1.06-3.30)	1.4
Rheumatoid/lupus/psoriasis	1.23	(1.12-1.35)	1.31	(1.14-1.51)	1.2
Other immunosuppressive condition‡	1.69	(1.21-2.34)	2.01	(1.25-3.25)	1.8

*Includes motor neurone disease, myasthenia gravis, multiple sclerosis, Parkinson's disease, cerebral palsy, quadriplegia, hemiplegia, malignant primary brain tumour and progressive cerebellar disease.
†Includes splenectomy, or spleen dysfunction (e.g. from sickle cell disease).
‡Includes HIV, conditions inducing permanent immunodeficiency (ever diagnosed), aplastic anaemia, and temporary immunodeficiency recorded within the past year.

UPDATE 3: 29 JUNE 2020

In a prospective cohort study of all 800 cancer patients from a network of UK cancer centres who presented to hospital during 18 March to 26 April 2020 with symptomatic test-positive Covid-19, 226 (25%) died, almost all (211) because of the infection [3.6]. After adjustment for age, gender and comorbidities, there was no significant association of mortality either with chemotherapy in the preceding four weeks, or with other treatment modalities. However, little can be drawn from this in relation to our model of vulnerability because entry to the study was restricted to symptomatic Covid-19 presenting to hospital, and the risk estimates did not account for type, duration or severity of cancer.

A multicentre matched cohort study in Spain compared the risk of severe outcomes (death, invasive ventilation, admission to intensive care or serious complications) in 456 rheumatic patients with Covid-19 confirmed by PCR testing and 456 controls, also with confirmed Covid-19, but with no rheumatic disease [3.7]. After adjustment for sex, age and various comorbidities, risk was elevated in those with autoimmune/immune-mediated diseases (AI/IMD) such as SLE, Sjögren's syndrome, systemic sclerosis, polymyalgia rheumatica and vasculitis (OR 1.98, 95%CI 1.15-3.41), but not in those with inflammatory arthritides such as rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. The results cannot be used to refine our currently adopted risk estimate for rheumatoid/lupus/psoriasis because of uncertainties about the selection of patients for the Covid-19 testing that qualified them for entry to the study. However, the findings suggest that within that broad diagnostic category, the vulnerability associated with AI/IMD may be greater than that associated with inflammatory arthritis.

UPDATE 4: 16 JULY 2020

The updated report from the OS study [4.1] indicates a need to modify slightly some of the adopted risk estimates in Table Y1. Table Y2 shows the HRs in the new report and indicates the relative risks that have now been adopted (those that have changed being marked by double asterisks).

Table Y2. Adjusted hazard ratios for other comorbidities from the updated report of the OS cohort [4.1], and relative risk estimates taken forward to risk model

Comorbidity	Follow-up censored at 6.5.20		Follow-up censored at 6.4.20		RR adopted for risk model
	HR	(95%CI)	HR	(95%CI)	
Non-haematological cancer					
None	1		1		
Diagnosed <1 year ago	1.72	(1.50-1.97)	1.66	(1.27-2.16)	1.7**
Diagnosed 1-4.9 years ago	1.15	(1.05-1.27)	1.34	(1.13-1.60)	1.2
Diagnosed ≥5 years ago	0.96	(0.91-1.03)	0.92	(0.81-1.04)	1.0
Haematological malignancy					
None	1		1		
Diagnosed <1 year ago	2.82	(2.09-3.81)	2.22	(1.15-4.27)	2.8**
Diagnosed 1-4.9 years ago	2.47	(2.06-2.96)	3.50	(2.61-4.69)	2.5**
Diagnosed ≥5 years ago	1.62	(1.39-1.88)	1.45	(1.07-1.98)	1.6**
Liver disease	1.75	(1.51-2.03)	1.92	(1.48-2.49)	1.8**
Chronic neurological disease other than stroke or dementia*	2.58	(2.38-2.79)	2.26	(1.91-2.68)	2.6**
Organ transplant	3.55	(2.79-4.52)	2.57	(1.60-4.13)	3.6**
Asplenia†	1.34	(0.98-1.83)	1.87	(1.13-3.11)	1.4
Rheumatoid/lupus/psoriasis	1.19	(1.11-1.27)	1.29	(1.14-1.46)	1.2
Other immunosuppressive condition‡	1.70	(1.34-2.16)	1.98	(1.32-2.96)	1.8

*Includes motor neurone disease, myasthenia gravis, multiple sclerosis, Parkinson's disease, cerebral palsy, quadriplegia, hemiplegia, and progressive cerebellar disease.
†Includes splenectomy, or spleen dysfunction (e.g. from sickle cell disease).
‡Includes HIV, conditions inducing permanent immunodeficiency (ever diagnosed), aplastic anaemia, and temporary immunodeficiency recorded within the past year.
**Adopted relative risk estimates that have changed

SECTION THREE: ESTIMATION OF INDIVIDUAL VULNERABILITY

Covid-age

Using the relative risk estimates that have been derived in the preceding sections of this report, it is possible to estimate the vulnerability of an individual should he or she at some stage contract Covid-19.

A major determinant of risk is age. Using the risk estimate for age from Section A, an increase in age of n years carries a relative risk of 1.0945^n. This implies that a relative risk, R, is equivalent to that from an increase in age of (log R)/(log 1.0945) years. Applying this formula, Table Z1 expresses the relative risks that are currently adopted for risk factors other than age as the additional years of age that would give an equivalent relative risk.

The analyses that were used to generate these risk estimates assumed that relative risks from different risk factors multiply, which in the absence of persuasive evidence to the contrary, seems a reasonable assumption. With that assumption, an individual's vulnerability can be assessed from Table Z1 by summing the added age equivalent for each risk factor that applies. For example, an Asian woman aged 50 with poorly controlled Type 2 diabetes would have an estimated vulnerability equivalent to that of a healthy white man aged 50 - 8 + 4 + 8 = 54 years.

We designate the age at which a healthy white man would have equivalent vulnerability, a person's "Covid-19-age".

Table Z1. Vulnerability from risk factors expressed as equivalence to added years of age

Risk factor	Relative risk	Equivalent added years of age	Robustness of risk estimate
Female sex	0.5	-8	Robust
Ethnicity			
Asian or Asian British	1.5	4	Moderately robust
Black	1.7	6	Moderately robust
Mixed	1.6	5	Provisional
Other non-white	1.3	3	Provisional
Body mass index (Kg/m^2)			
30-34.9	1.4	4	Provisional
35-39.9	1.6	5	Provisional
≥40	2.4	10	Provisional
Asthma			
Mild (no requirement for oral corticosteroids in past year)	1.1	1	Moderately robust
Severe (requiring oral corticosteroids in past year)	1.4	4	Moderately robust
Diabetes			
Type 1			
HbA1≤58 mmol/mol in past year	2.0	8	Moderately robust
HbA1>58 mmol/mol in past year	2.7	11	Moderately robust
HbA1c unknown	3.3	13	Moderately robust
Type 2 and other			
HbA1≤58 mmol/mol in past year	1.5	4	Moderately robust
HbA1>58 mmol/mol in past year	2.0	8	Moderately robust
HbA1c unknown	2.3	9	Moderately robust
Heart failure	2.2	9	Provisional
Other chronic heart disease	1.3	3	Provisional
Cerebrovascular disease	2.2	9	Provisional
Chronic respiratory disease (excluding asthma)	1.9	7	Moderately robust

Chronic kidney disease*	1.7	6	Moderately robust
Non-haematological cancer			
Diagnosed <1 year ago	1.6	5	Provisional
Diagnosed 1-4.9 years ago	1.2	2	Provisional
Diagnosed ≥5 years ago	1	0	Provisional
Haematological malignancy			
Diagnosed <1 year ago	3.5	14	Provisional
Diagnosed 1-4.9 years ago	3.1	13	Provisional
Diagnosed ≥5 years ago	1.9	7	Provisional
Liver disease	1.6	5	Provisional
Chronic neurological disease other than stroke or dementia**	2.5	10	Provisional
Organ transplant	4.3	16	Provisional
Spleen diseases†	1.4	4	Provisional
Rheumatoid/lupus/psoriasis	1.2	2	Provisional
Other immunosuppressive condition‡	1.8	7	Provisional

*Glomerular filtration rate <60mL/min/1.73m2, as estimated from the most recent serum creatinine measurement.
**Includes motor neurone disease, myasthenia gravis, multiple sclerosis, Parkinson's disease, cerebral palsy, quadriplegia, hemiplegia and progressive cerebellar disease.
†Includes splenectomy, or spleen dysfunction (e.g. from sickle cell disease).
‡Includes HIV, conditions inducing permanent immunodeficiency (ever diagnosed), aplastic anaemia, and temporary immunodeficiency recorded within the past year.

Case-fatality rates by Covid-age

To understand how Covid-age relates to case-fatality rate, an estimate is needed of the case-fatality rate for healthy white men at a specified age. Estimated relative risks by age can then be applied to estimate case-fatality at other ages.

As yet, no direct data are available from the UK on case-fatality by sex and age for all cases of Covid-19 including asymptomatic infection, or even for cases of symptomatic disease. Our starting point, therefore, was a report by Ferguson and colleagues [9], which presented estimates of infection fatality ratio (case-fatality rate) by sex and age, drawing on findings from a study by Verity and colleagues [10].

In the Ferguson report, the case fatality rate at 40-49 years of age in men and women combined was estimated to be 1.5 per 1000. Assuming a relative risk of 0.5 in women as compared with men (see Section B), this would imply a case fatality rate in men of 1.5*2/1.5 = 2 per thousand.

A limited check on the plausibility of this figure is possible using data on fatality rates among patients in the ISARIC study, who were admitted to British hospitals with Covid-19 [3]. From measurements of the lengths of bars in a bar chart, among men aged 40-49 years, approximately 22 had died by the time that data collection was censored, 241 had been discharged from hospital alive, and 58 were still in hospital. This implies a case-fatality rate of 1000*22/(22+241) = 83 per thousand among those whose final outcome was known. It is likely, however, that the true case fatality rate is somewhat higher than this because the cohort members who were still in hospital when data collection was censored, selectively included sicker patients who had failed to recover quickly. If the estimated fatality rate of 2 per 1000 in the general population were correct, a fatality rate of, say, 100 per 1000 in hospitalised cases, would imply that approximately one in fifty cases in the community lead to hospital admission. That figure seems plausible, for a relatively young age group, although there are major uncertainties about the frequency of asymptomatic infection.

Tentatively, therefore, we assumed an overall case-fatality rate of 2 per 1000 in men aged 45 (just above the mid-point of the age range under consideration), and that on average, the Covid-age of men with a true age of 45 might be 47 years. Thus, we assigned a case fatality rate of 2 per 1000 to a Covid-age of 47. Rates at other ages were then calculated by applying the previously determined relative risk of 1.0945 for each additional year of age (see Section A). Results are summarised in Table Z2.

In view of the many assumptions in these estimates of age-specific case fatality, we emphasise that they are subject to substantial uncertainty, and should be regarded only as provisional. A particular source of uncertainty is the unknown frequency of asymptomatic infection in the general population.

Table Z2. Relative risks of mortality from Covid-19 and estimated case fatality rates in healthy white males by age

Age (years)	Estimated risk relative to that at age 47 years (healthy white males)	Estimated case-fatality rate per 1000 in cases of Covid-19 infection (healthy white males)
20	0.1	0.2
25	0.1	0.3
30	0.2	0.4
35	0.3	0.7
40	0.5	1.1
45	0.8	1.7
47	1.0	2.0
50	1.3	2.6
52	1.6	3.1
54	1.9	3.8
56	2.3	4.5
58	2.7	5.4
60	3.2	6.5
62	3.9	7.7
64	4.6	9.3
66	5.6	11
68	6.7	13
70	8.0	16
72	9.6	19
74	11.5	23
76	13.7	27
78	16.4	33
80	19.7	39

UPDATE 3: 29 JUNE 2020

A national analysis of mortality from Covid-19 in Belgium during 8 March to 9 May 2020, in conjunction with estimated infection rates, suggested an infection fatality rate of 2.9 per 1000 among men aged 45-64 years [3.8]. It is unclear how reliably infection rates were estimated, and the fatality rate is for all men in the age band, including those with comorbidities. However, the finding is broadly consistent with our guarded estimate that case fatality among healthy men increases from 0.8 per 1000 at age 45 to 4.6 per 1000 at age 64.

UPDATE 4: 16 JULY 2020

In accordance with the rationale set out in the updates to Section 2, we have revised our adopted risk estimates as set out in Table Z3.

Table Z3. Vulnerability from risk factors expressed as equivalence to added years of age

Risk factor	Relative risk	Equivalent added years of age**	Robustness of risk estimate
Female sex	0.6	-5	Moderately robust
Ethnicity			
Asian or Asian British	1.5	4	Moderately robust
Black	1.7	5	Moderately robust
Mixed	1.4	3	Provisional
Other non-white	1.3	3	Provisional
Body mass index (Kg/m^2)			
30-34.9	1.3	3	Provisional
35-39.9	1.6	5	Provisional
≥40	2.4	9	Provisional
Hypertension (according to actual age)			
Age 20-26 years	3.3-3.6	12	Provisional
Age 27-33 years	3.0-3.3	11	Provisional
Age 34-39 years	2.7-2.9	10	Provisional
Age 40-44 years	2.4-2.6	9	Provisional
Age 45-49 years	2.2-2.4	8	Provisional
Age 50-54 years	2.0-2.1	7	Provisional
Age 55-57 years	1.8-1.9	6	Provisional
Age 58-61 years	1.6-1.8	5	Provisional
Age 62-64 years	1.5-1.6	4	Provisional
Age 65-67 years	1.3-1.4	3	Provisional
Age 68-70 years	1.2-1.3	2	Provisional
Age 71-72 years	1.1	1	Provisional
Age ≥73 years	1	0	Provisional
Heart failure	2.2	8	Provisional
Other chronic heart disease	1.3	3	Provisional
Cerebrovascular disease	2.2	8	Provisional

Asthma			
Mild (no requirement for oral corticosteroids in past year)	1.1	1	Moderately robust
Severe (requiring oral corticosteroids in past year)	1.4	3	Moderately robust
Chronic respiratory disease (excluding asthma)	1.9	6	Moderately robust
Diabetes			
Type 1			
HbA1≤58 mmol/mol in past year	2.0	7	Moderately robust
HbA1>58 mmol/mol in past year	2.7	10	Moderately robust
HbA1c unknown	3.3	12	Moderately robust
Type 2 and other			
HbA1≤58 mmol/mol in past year	1.5	4	Moderately robust
HbA1>58 mmol/mol in past year	2.0	7	Moderately robust
HbA1c unknown	2.3	8	Moderately robust
Chronic kidney disease			
Estimated GFR 30-60 mL/min	1.5	4	Moderately robust
Estimated GFR < 30 mL/min	3.0	11	Moderately robust
History of dialysis or end-stage renal failure	3.7	13	Moderately robust
Non-haematological cancer			
Diagnosed <1 year ago	1.7	5	Provisional
Diagnosed 1-4.9 years ago	1.2	2	Provisional
Diagnosed ≥5 years ago	1	0	Provisional
Haematological malignancy			
Diagnosed <1 year ago	2.8	10	Provisional
Diagnosed 1-4.9 years ago	2.5	9	Provisional
Diagnosed ≥5 years ago	1.6	5	Provisional
Liver disease	1.8	6	Provisional
Chronic neurological disease other than stroke or dementia*	2.6	9	Provisional
Organ transplant	3.6	12	Provisional
Spleen diseases†	1.4	3	Provisional
Rheumatoid/lupus/psoriasis	1.2	2	Provisional

Other immunosuppressive condition‡	1.8	6	Provisional

*Includes motor neurone disease, myasthenia gravis, multiple sclerosis, Parkinson's disease, cerebral palsy, quadriplegia, hemiplegia and progressive cerebellar disease.
†Includes splenectomy, or spleen dysfunction (e.g. from sickle cell disease).
‡Includes HIV, conditions inducing permanent immunodeficiency (ever diagnosed), aplastic anaemia, and temporary immunodeficiency recorded within the past year.
**Added years for hypertension are calculated from relative risks before rounding

The estimated case-fatality rates (both sexes and all ethnic groups) in the new report based on data from New York City [4.3] of 1.2 per 1000 at ages 25-44 years and 9.4 per 1000 at ages 45-64 years are broadly consistent with our previous estimate of 2 per 1000 for healthy white men aged 47 years. However, we have identified a need to adjust slightly our adopted relative risk by age. Taking account of this adjustment, Table Z4 sets out revised estimates of case-fatality in healthy white males by age.

Table Z4. Relative risks of mortality from Covid-19 and estimated case fatality rates in healthy white males by age

Age (years)	Estimated risk relative to that at age 47 years (healthy white males)	Estimated case-fatality rate per 1000 in cases of Covid-19 infection (healthy white males)
20	0.1	0.1
25	0.1	0.2
30	0.2	0.3
35	0.3	0.6
40	0.5	1.0
45	0.8	1.6
47	1.0	2.0
50	1.4	2.7
52	1.7	3.3
54	2.1	4.1
56	2.5	5.1
58	3.1	6.2
60	3.8	7.6
62	4.7	9.4
64	5.8	11.5
66	7.1	14.1
68	8.7	17.4
70	10.7	21.3
72	13.1	26.2
74	16.1	32.2
76	19.8	39.6
78	24.3	48.6
80	29.9	59.7

UPDATE 5: 27 JULY 2020

As described in Section 1, we are aware of growing suspicions that relative risks associated with some comorbidities may be higher in young adults and lower at older ages. Other than for hypertension, we do not as yet have usable quantitative estimates of any such variation in relative risks by age, but we highlight this as an uncertainty that should be taken into account when using the risk estimates in Table Z3. Other than for hypertension, those risk estimates should be viewed as averages across adults of all ages.

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