Nirmatrelvir plus ritonavir for treating COVID-19

Part review of TA878

Contains redacted PART 1 slides

Technology appraisal committee C

Chair: Stephen O'Brien

Evidence assessment group: School of Health and Related Research (ScHARR), Sheffield

Technical team: Anna Brett, Anuja Chatterjee, Adam Brooke, Ross Dent

Company: Pfizer

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Recap and Decision problem

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Recommendation for nirmatrelvir plus ritonavir

Nirmatrelvir plus ritonavir is recommended as an option for treating COVID-19 in adults, only if they:

- do not need supplemental oxygen for COVID-19 and

- have an increased risk for progression to severe COVID-19, as defined in the [independent advisory group report commissioned by the Department of Health and Social Care](). (McInnes report)

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Aim of review

Is nirmatrelvir plus ritonavir clinically and cost-effective in broader population than McInnes report?

DHSC Antiviral and Therapeutics Task force commissioned a report by John Edmund's (Edmund's report) to assess whether there are any groups that have a risk that is at least as high as McInnes groups (published 29 March 2023)

Company submitted additional evidence for nirmatrelvir plus ritonavir after final draft guidance issued to support expansion of the high-risk group definition

McInnes criteria for highest risk

↓

Age over 70, diabetes and obesity have same risk as lowest risk groups in McInnes report

↓

Company submitted evidence and request committee consider broadening recommendation for all age over 60+ or 18-59 with 1 risk factor

Key issues for discussion
Expansion of high-risk group definition

Issue	ICER impact	Population size impact and decision risk
Is nirmatrelvir plus ritonavir clinically and cost effective for people who are 70 years and over?	Moderate	High
Is nirmatrelvir plus ritonavir clinically and cost effective for any other groups?	Large	Very high

Final guidance and model recap

Unlike other risk factors age can be adjusted within the model framework

Final guidance section 3.6:

✓ Committee noted evidence at a subgroup level is limited and too uncertain to parameterise the model, additional functionality and input assumptions maybe needed

✓ Committee specified additional evidence needed to model age over 70 years

Model recap:
- The AG model does not include functionality to model individual subgroups split by the risk factors
- Unlike specific risk factors like diabetes or obesity, age can be adjusted by changing the starting age in the mild COVID-19 setting
  - This affects cost-effectiveness because average age in model is 55, so increasing eligibility to 70+ would increase average age → shorter time to accrue QALYs from avoiding mortality

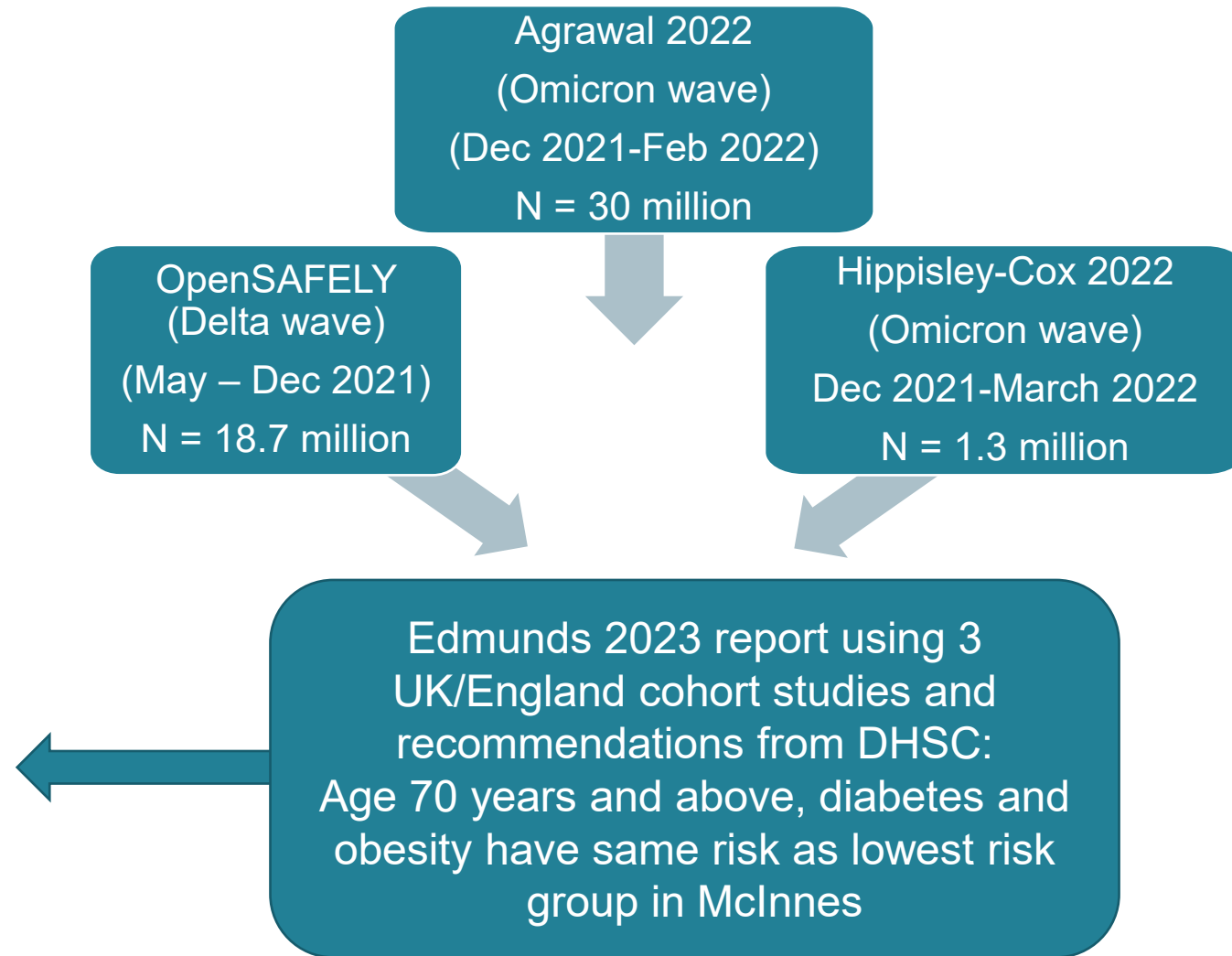Additional evidence provided by company include:
- Treatment specific (nirmatrelvir plus ritonavir) hospitalisation and mortality rates split by age
- Relative treatment effect of nirmatrelvir plus ritonavir (versus untreated/ standard care) in terms of hospitalisation and mortality rates split by age
  - Hospitalisation or death relative risk
  - All-cause mortality relative risk at 28 days

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McInnes definition and Edmunds report

McInnes: People more likely to develop severe COVID-19

Some people have a health condition that may increase their risk of getting seriously ill from COVID-19, such as:

- Down's syndrome
- certain types of cancer including leukaemia
- certain conditions affecting the blood, such as sickle cell disease
- people who have had a stem cell transplant
- kidney disease
- liver disease
- people who have had an organ transplant
- conditions affecting the immune system, such as HIV or AIDS, inflammatory conditions or immunodeficiency
- conditions affecting the brain or nerves (multiple sclerosis, motor neurone disease, Huntington's disease or myasthenia gravis).
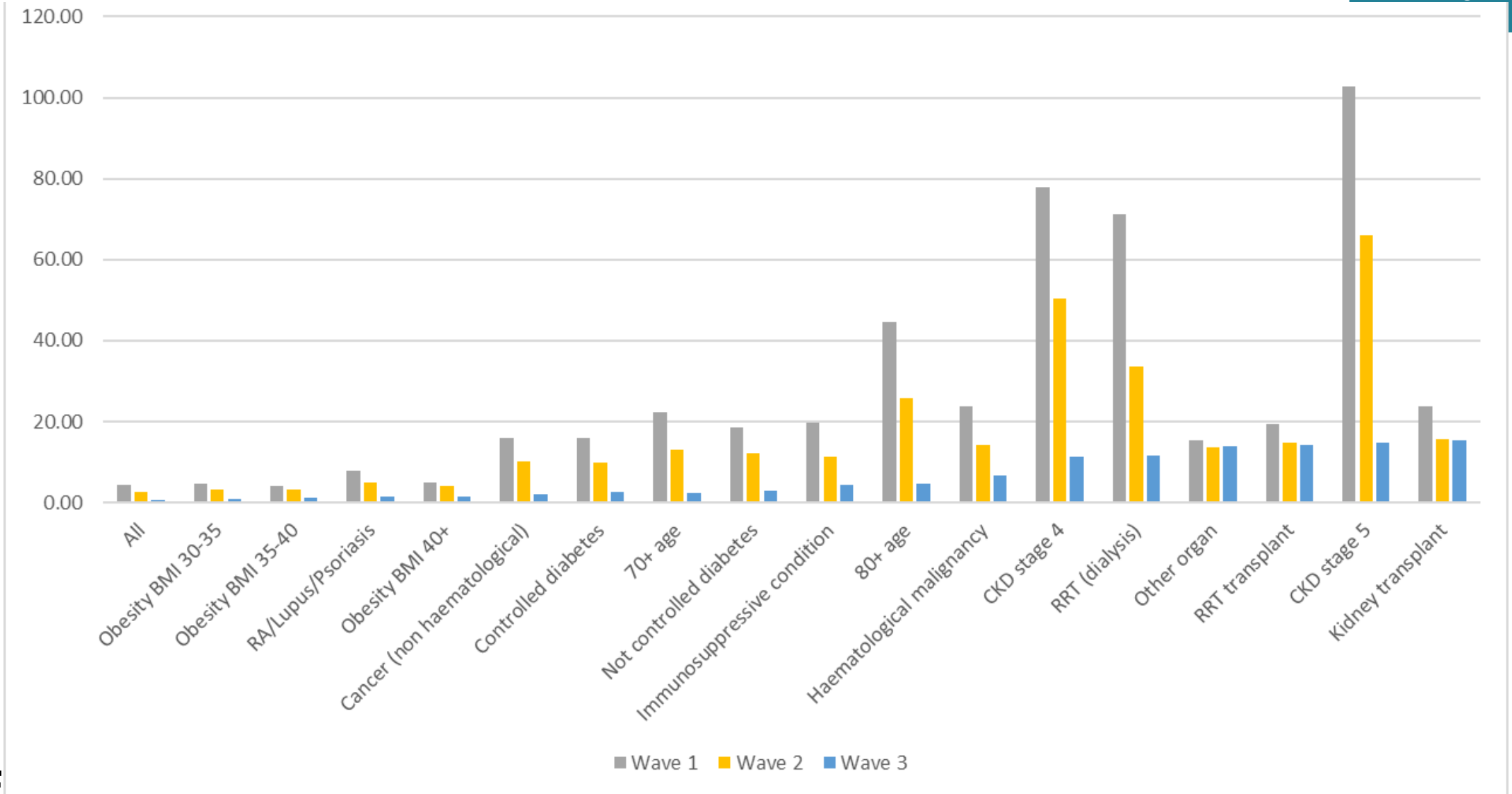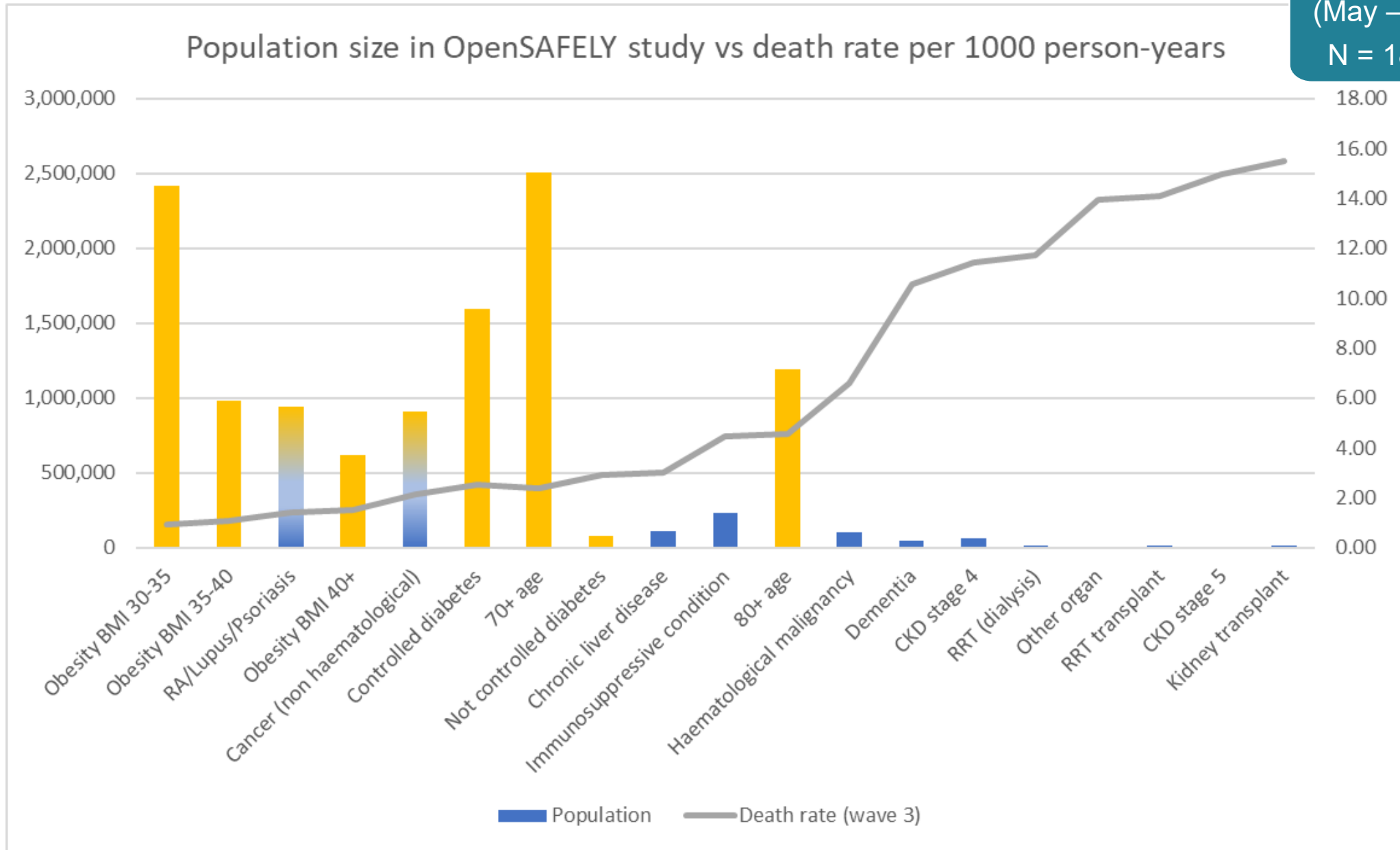
Agrawal 2022
(Omicron wave)
(Dec 2021-Feb 2022)
N = 30 million

OpenSAFELY
(Delta wave)
(May – Dec 2021)
N = 18.7 million

Hippisley-Cox 2022
(Omicron wave)
Dec 2021-March 2022
N = 1.3 million

Edmunds 2023 report using 3 UK/England cohort studies and recommendations from DHSC:
Age 70 years and above, diabetes and obesity have same risk as lowest risk group in McInnes

The full list of conditions is available in the independent advisory group report commissioned by the Department of Health and Social Care.

Evidence within Edmunds paper

Death rate per 1000 person years across waves

Legend: Wave 1 (grey), Wave 2 (yellow), Wave 3 (blue)

Categories: All, Obesity BMI 30-35, Obesity BMI 35-40, RA/Lupus/Psoriasis, Obesity BMI 40+, Cancer (non haematological), Controlled diabetes, 70+ age, Not controlled diabetes, Immunosuppressive condition, 80+ age, Haematological malignancy, CKD stage 4, RRT (dialysis), Other organ, RRT transplant, CKD stage 5, Kidney transplant

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Death rate during the Delta wave from OpenSAFELY

Population size in OpenSAFELY study vs death rate per 1000 person-years

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Adjusted rate associated with hospitalisation or death

Agrawal 2022
(Omicron wave)
(Dec 2021-Feb 2022)
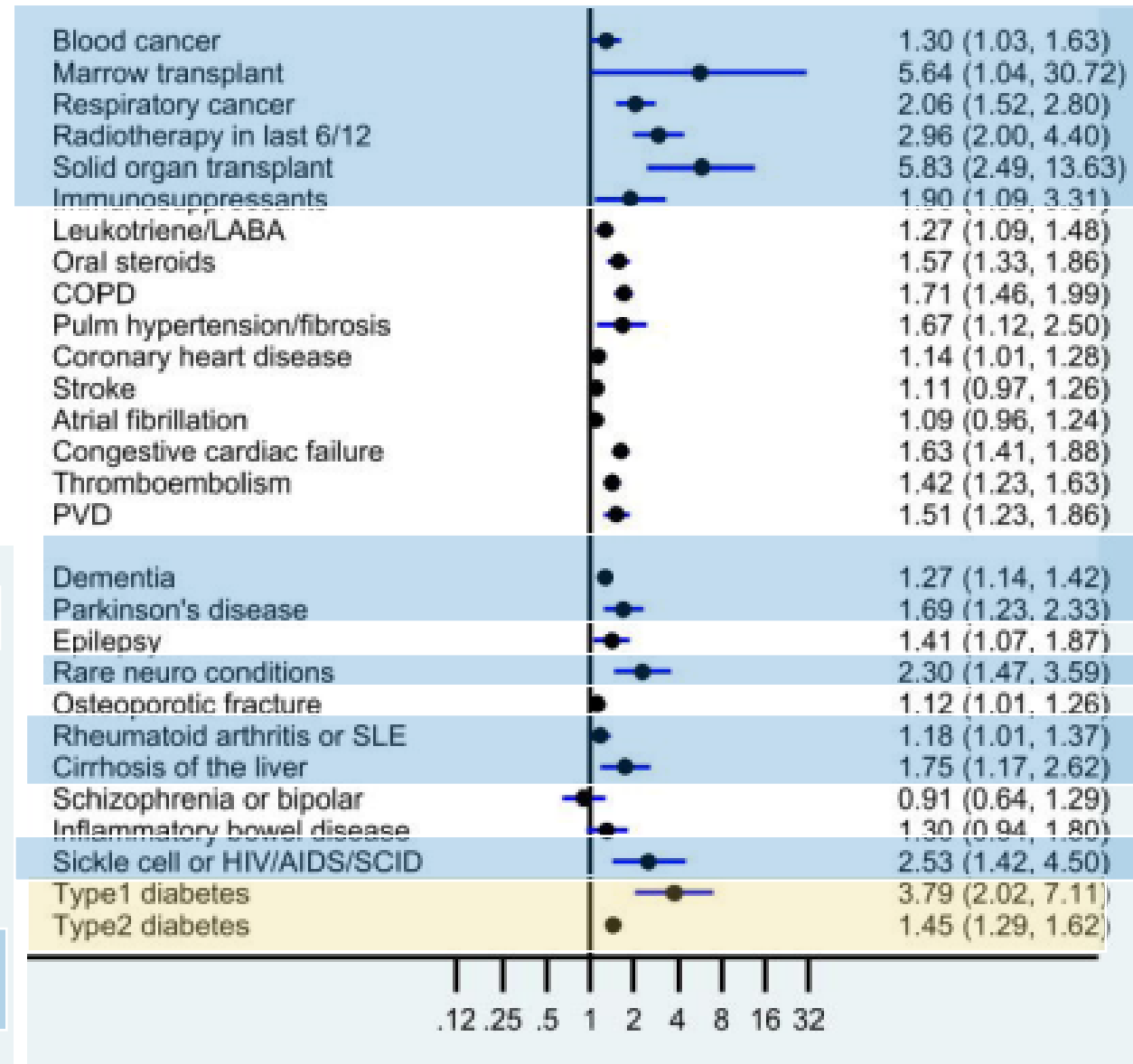N = 30 million

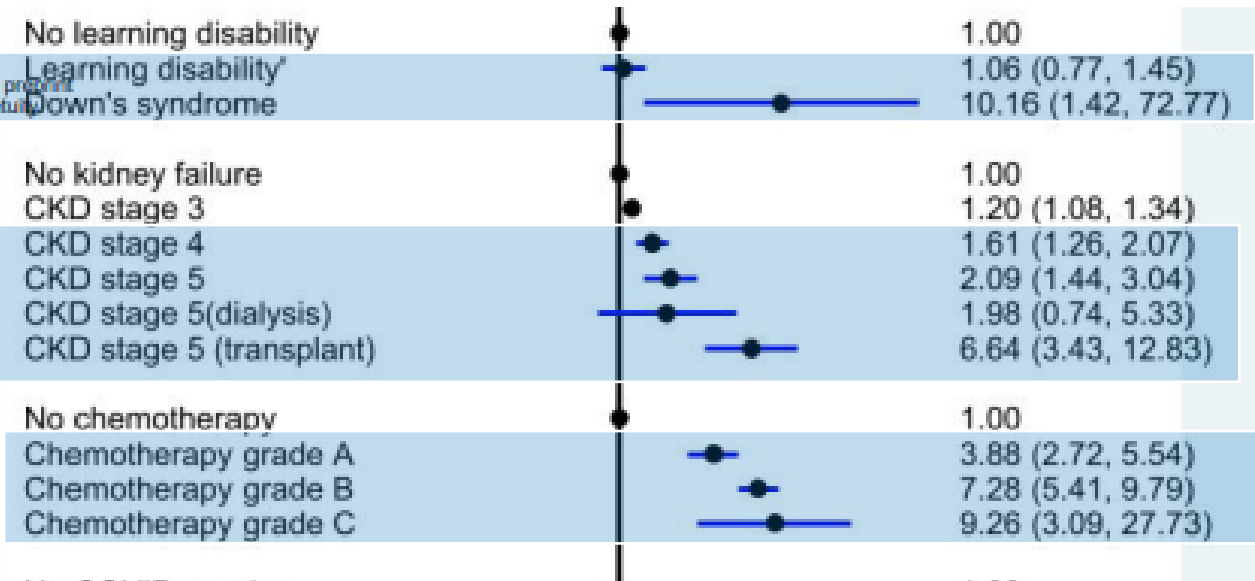# Adjusted rate associated with hospitalisation or death
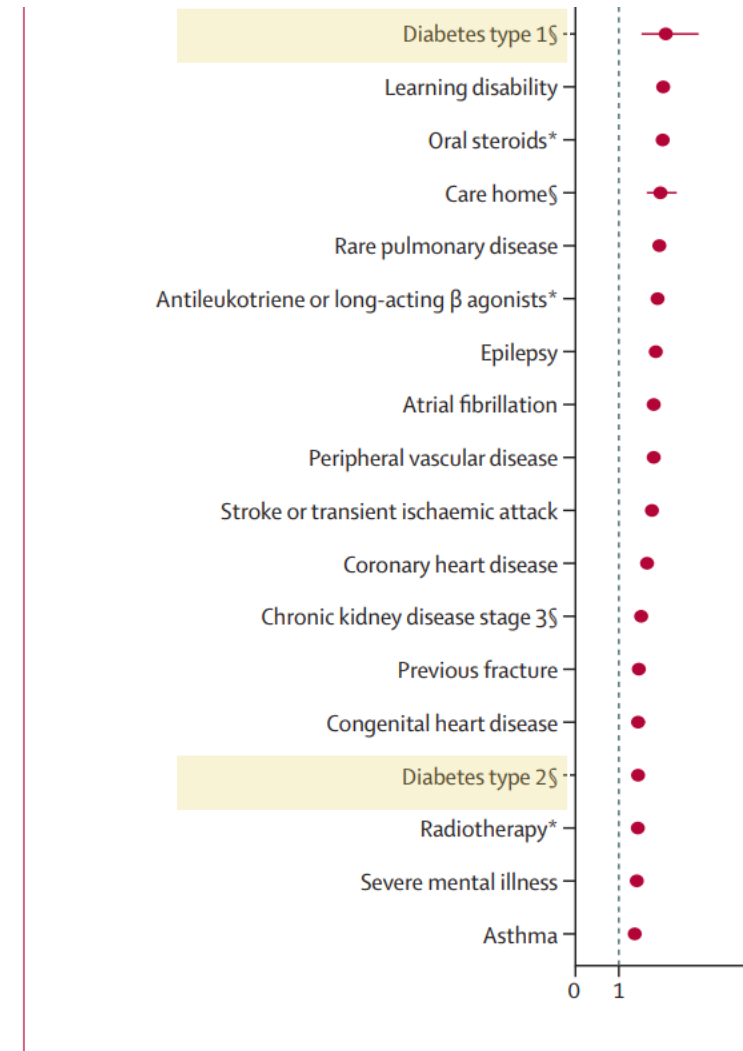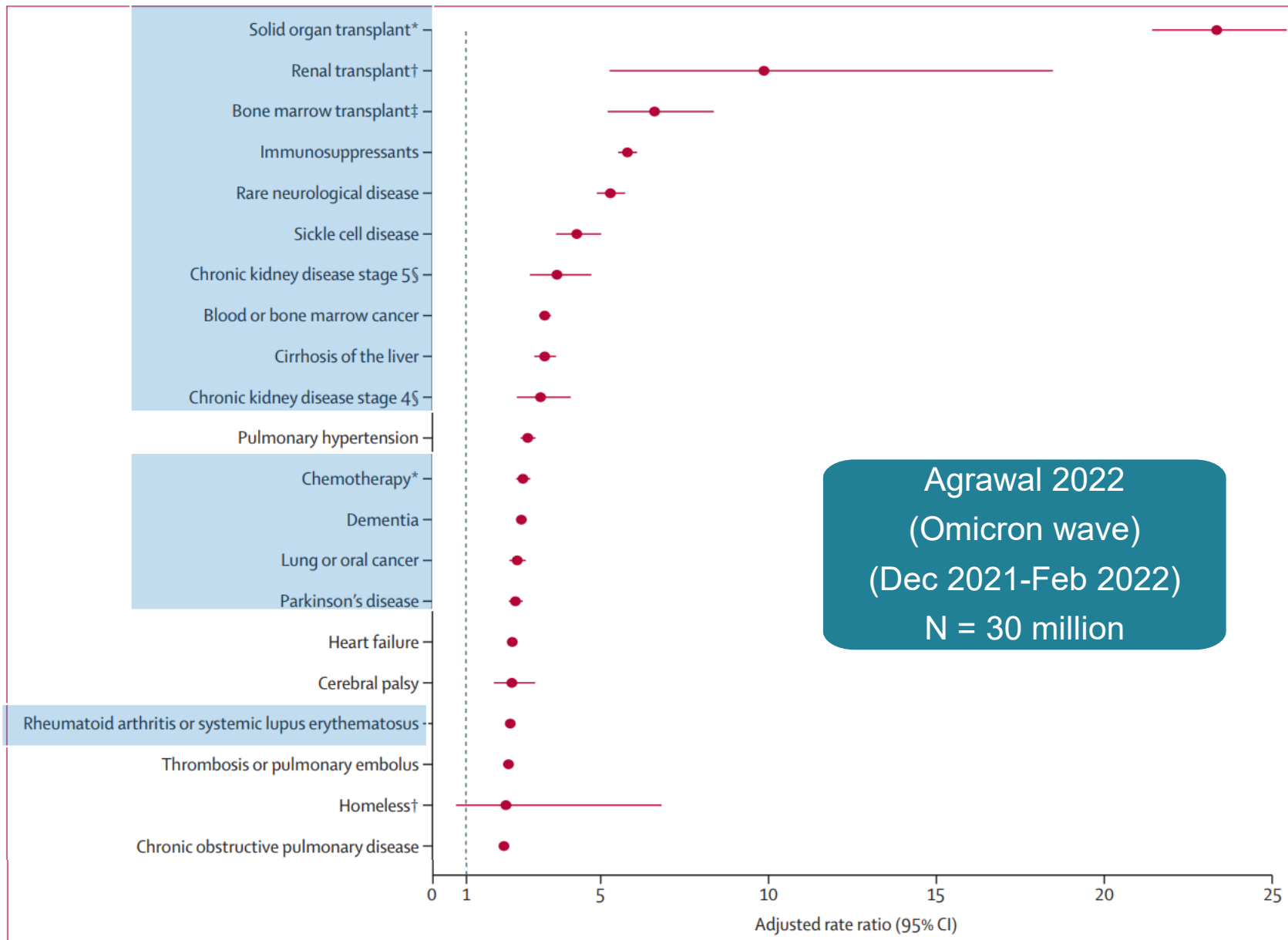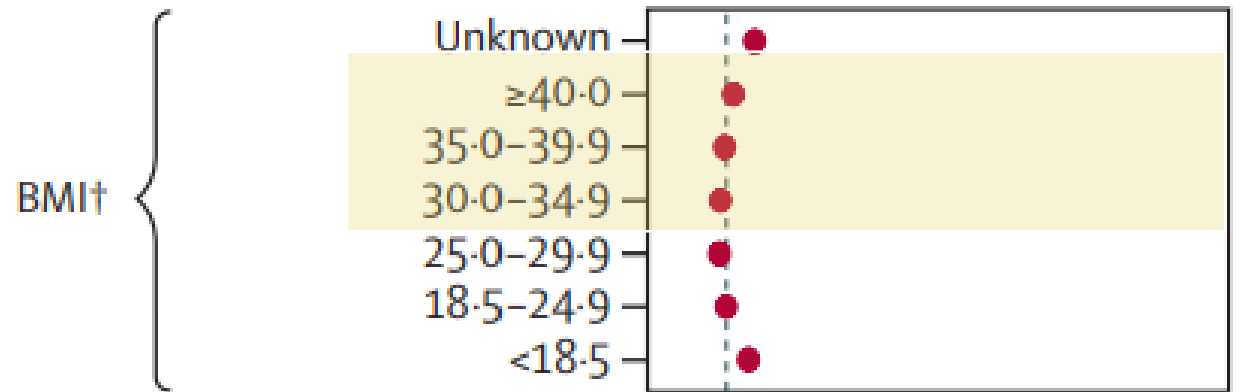
Agrawal 2022
(Omicron wave)
(Dec 2021-Feb 2022)
N = 30 million
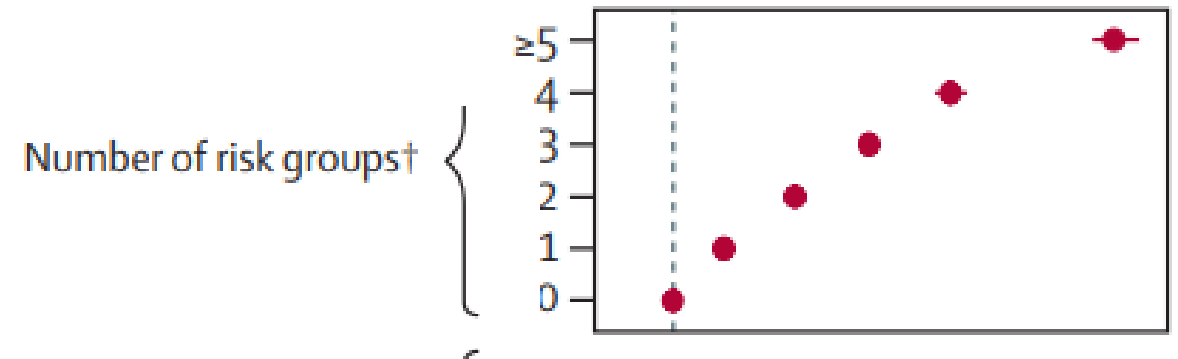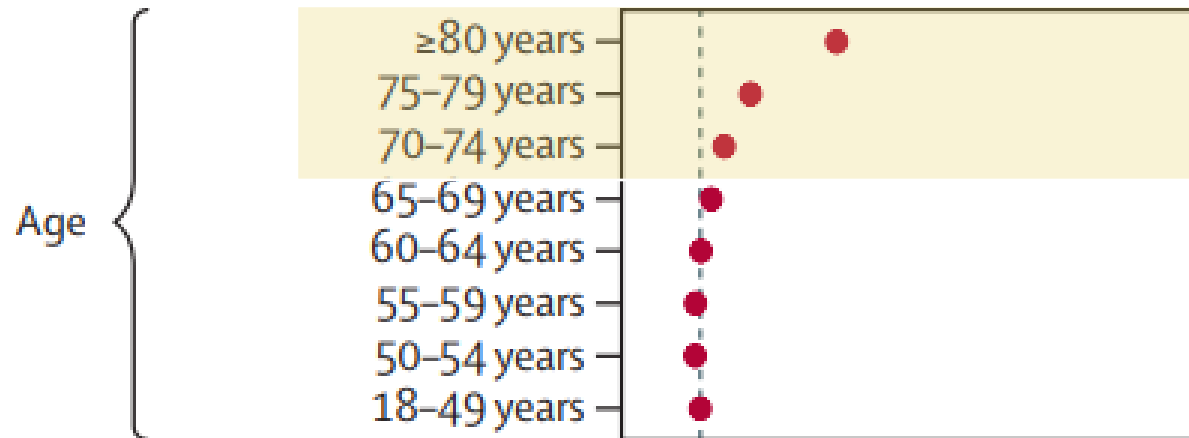
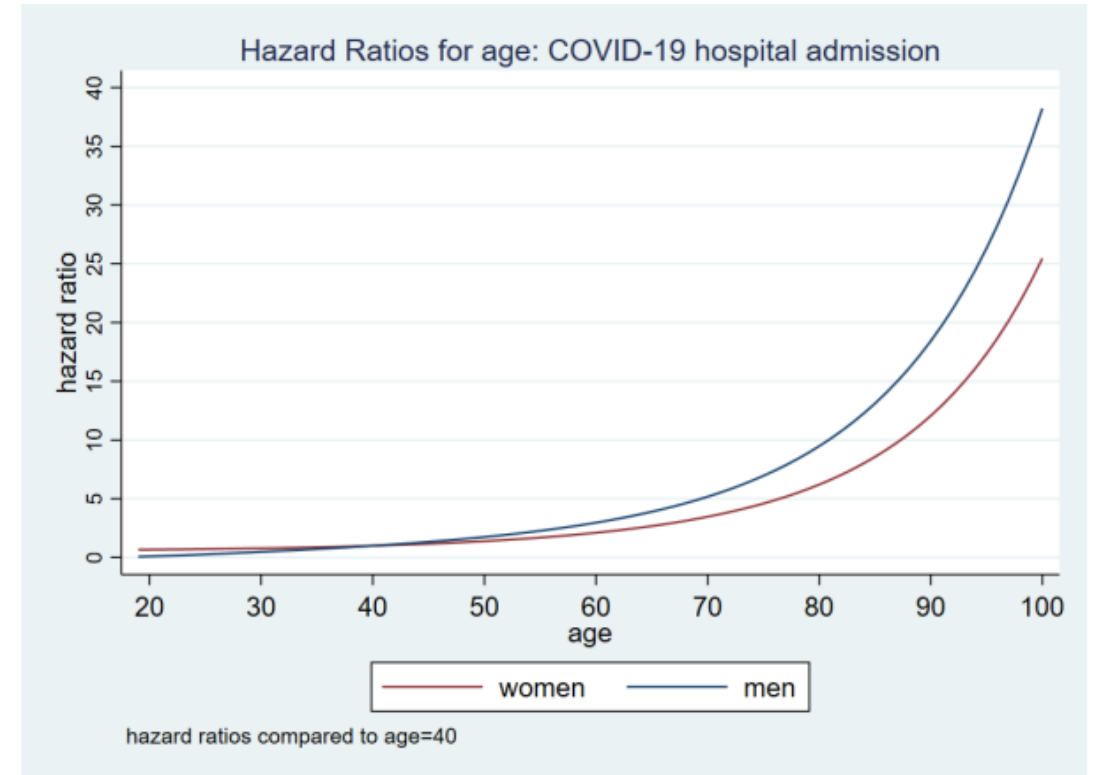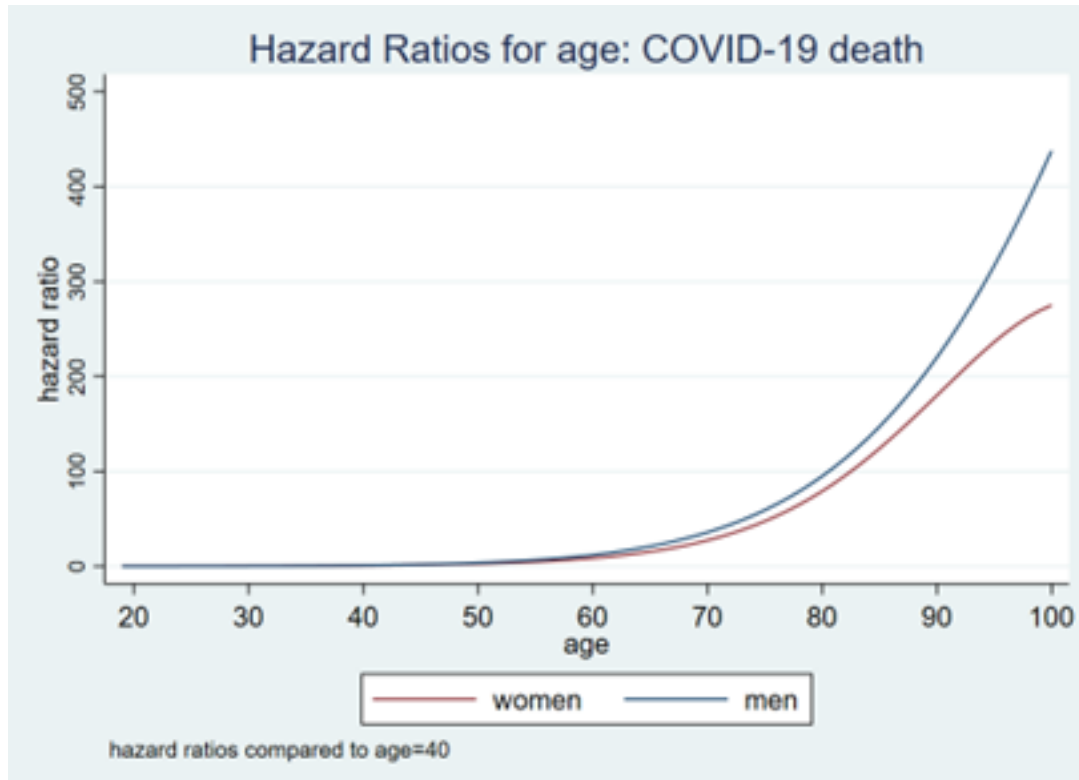# Adjusted HR of COVID-19 death in women (Q-COVID4)

Hippisley-Cox 2022
(Omicron wave)
Dec 2021-March 2022
N = 1.3 million

	HR (95% CI)
No learning disability	1.00
Learning disability'	1.06 (0.77, 1.45)
Down's syndrome	10.16 (1.42, 72.77)
No kidney failure	1.00
CKD stage 3	1.20 (1.08, 1.34)
CKD stage 4	1.61 (1.26, 2.07)
CKD stage 5	2.09 (1.44, 3.04)
CKD stage 5(dialysis)	1.98 (0.74, 5.33)
CKD stage 5 (transplant)	6.64 (3.43, 12.83)
No chemotherapy	1.00
Chemotherapy grade A	3.88 (2.72, 5.54)
Chemotherapy grade B	7.28 (5.41, 9.79)
Chemotherapy grade C	9.26 (3.09, 27.73)

	HR (95% CI)
Blood cancer	1.30 (1.03, 1.63)
Marrow transplant	5.64 (1.04, 30.72)
Respiratory cancer	2.06 (1.52, 2.80)
Radiotherapy in last 6/12	2.96 (2.00, 4.40)
Solid organ transplant	5.83 (2.49, 13.63)
Immunosuppressants	1.90 (1.09, 3.31)
Leukotriene/LABA	1.27 (1.09, 1.48)
Oral steroids	1.57 (1.33, 1.86)
COPD	1.71 (1.46, 1.99)
Pulm hypertension/fibrosis	1.67 (1.12, 2.50)
Coronary heart disease	1.14 (1.01, 1.28)
Stroke	1.11 (0.97, 1.26)
Atrial fibrillation	1.09 (0.96, 1.24)
Congestive cardiac failure	1.63 (1.41, 1.88)
Thromboembolism	1.42 (1.23, 1.63)
PVD	1.51 (1.23, 1.86)
Dementia	1.27 (1.14, 1.42)
Parkinson's disease	1.69 (1.23, 2.33)
Epilepsy	1.41 (1.07, 1.87)
Rare neuro conditions	2.30 (1.47, 3.59)
Osteoporotic fracture	1.12 (1.01, 1.26)
Rheumatoid arthritis or SLE	1.18 (1.01, 1.37)
Cirrhosis of the liver	1.75 (1.17, 2.62)
Schizophrenia or bipolar	0.91 (0.64, 1.29)
Inflammatory bowel disease	1.30 (0.94, 1.80)
Sickle cell or HIV/AIDS/SCID	2.53 (1.42, 4.50)
Type1 diabetes	3.79 (2.02, 7.11)
Type2 diabetes	1.45 (1.29, 1.62)

.12 .25 .5 1 2 4 8 16 32

Adjusted hazard ratios for age and risk of COVID-19 deaths/hospital admissions derived from the living risk prediction algorithm QCOVID

Hazard Ratios for age: COVID-19 death

hazard ratios compared to age=40

Hazard Ratios for age: COVID-19 hospital admission

hazard ratios compared to age=40

✓ QCOVID study controlled for other covariates when calculating hazard ratios for age related risk; therefore, the data represents the impact of age on mortality and hospitalisation alone

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Updated clinical evidence

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Company requested subgroup data from PANORAMIC

Company comments

- Preferred high-risk definition: includes all aged over 60 and between 18-59 year with at least one pre-existing health condition
- Rationale for wider cohort:
  - QCOVID algorithm and ISARIC report shows age is an independent risk factor and age 50+ is at least as comparable to the McInnes defined population
  - JCVI's routinely used criteria is to recommended access to the COVID-19 vaccine for ages 50 years and above - Similar criteria should also apply for treatment of COVID-19
- Data has been provided from PANORAMIC and the nirmatrelvir plus ritonavir's EPIC-HR trial. Data from EPIC-SR could not be provided due to low event numbers.

Table: PANORAMIC and EPIC-HR trial data

	70 years+*	65 years+*	60 years+* EPIC-HR full trial	PANORAMIC Full trial 50 years+*
Mean age non-hospital setting	▮	▮	▮	56.6
Baseline hospitalisation rate from PANORAMIC (Placebo arm)	▮	▮	▮	0.77%
Relative risk of death from any cause through day 28 (95% CI)	▮	▮	▮	0.15 (0.001-0.63)
Relative risk of hospitalisation or death (95% CI)	▮	▮	▮	0.14 (0.07-0.27)

* denotes: Also includes 18–59 years with ≥1 high risk condition

NICE CI, Confidence interval; JCVI, Joint Committee on Vaccination and Immunisation

AG comments on PANORAMIC and EPIC HR data

AG comments:

- Results presented by Pfizer which included younger age groups were deemed inappropriate. Individual age groups should have been modelled to generate consistent and unbiased outcomes (for example 65-69 instead of 65 years and below). (See Table 1 in AG critique)
- To model 70+, AG's preference was to use the mean age groups for community and hospital settings and the hospitalisation and 28 day mortality rates for the standard care arm from PANORAMIC
- For relative treatment effect of nirmatrelvir/ritonavir compared with standard care, two different analysis were done. One used COVID-NMA outcomes and the second used publicly available data from EPIC-SR. For the EPIC-SR scenario, no mortality benefit was assumed for nirmatrelvir/ritonavir.

NICE tech team comments:

- EPIC-SR is a relevant trial because it is reflective of a vaccinated population. As of March 2023, 90% of people between 70-74 were vaccinated with the COVID-19 third/booster dose in England. The relative treatment effect of nirmatrelvir plus ritonavir compared with standard care from EPIC-SR is therefore relevant for decision making. As stated in final guidance, the preliminary outcomes showed non-significant reduction in hospitalisation rates in the vaccinated high-risk subgroup.

NICE CI, Confidence interval; JCVI, Joint Committee on Vaccination and Immunisation

Cost-effectiveness results

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FG base case and scenarios considered by AG

	High-risk population (as in final guidance (FG))	70 years and over – Scenario 1	70 years and over – Scenario 2	High-risk population (as in FG) plus 70 years and over - Scenario 3	The Pfizer analysis deemed by the EAG to be the most representative of NICE's request
Mean age of hospitalised patients (years)	55.0	█████	████	70.0	████
Mean age of non-hospitalised patients (years)	55.0	█████	████	65.0	████
Baseline hospitalisation rate (with standard care)	2.82%	█████	████	2.82%	████
Baseline 28-day mortality rate (with standard care)	0.68%	█████	████	0.68%	█████ / ████
Nirmatrelvir/ritonavir hospitalisation or death relative risk	Median: 0.13 95% CI: 0.07-0.27 Mean: 0.14	Median: 0.13 95% CI: 0.07-0.27 Mean: 0.14	EPIC-SR: Median: 0.43 95% CI: 0.11-1.64 Mean: 0.55	Median: 0.13 95% CI: 0.07-0.27 Mean: 0.14	████
Nirmatrelvir/ritonavir all-cause day 28 mortality relative risk	Median: 0.04 95% CI: 0.00-0.63 Mean: 0.15	Median: 0.04 95% CI: 0.00-0.63 Mean: 0.15	Assumption: 1	Median: 0.04 95% CI: 0.00-0.63 Mean: 0.15	████

Please see AG critique for further details and input parameter assumptions; CI, Confidence interval

AG results assuming mean efficacy

Table: Deterministic incremental results for scenarios 1 to 3

Technology	Total costs (£)	Total QALYs	ICER versus SoC (£/QALY)	NMB (£20,000 / QALY)	NMB (£30,000 / QALY)
Scenario 1 (baseline rates from PANORAMIC + efficacy data from **COVID-NMA**)					
SoC	711	6.51	-	-	-
Nirmatrelvir/ritonavir	1761	6.55	26,381	-254	144
Scenario 2 (baseline rates from PANORAMIC + efficacy data from **EPIC-SR** with assumptions)					
SoC	711	6.51	-	-	-
Nirmatrelvir/ritonavir	1811	6.53	61,454	-742	-563
Scenario 3 (baseline rates from previous high-risk analyses, efficacy data from **COVID-NMA** and starting ages of 70 and 65 for hospitalised and non-hospitalised patients)					
SoC	1053	9.97	-	-	-
Nirmatrelvir/ritonavir	1805	10.10	5516	1975	3339

ICERs ranging from below £20000 per QALY gained to above £50,000 per QALY gained.

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ICER, Incremental cost effectiveness ratio; QALY, Quality adjusted life years; NMB, Net monetary benefit; SoC, Standard care

AG results assuming low efficacy

Table: Deterministic incremental results for scenarios 1 to 3

Technology	Total costs (£)	Total QALYs	ICER versus SoC (£/QALY)	NMB (£20,000 / QALY)	NMB (£30,000 / QALY)
Scenario 1 (baseline rates from PANORAMIC + efficacy data from **COVID-NMA**)					
SoC	711	6.51	-	-	-
Nirmatrelvir/ritonavir	1766	6.54	33,615	-427	-113
Scenario 2 (baseline rates from PANORAMIC + efficacy data from **EPIC-SR** with assumptions)					
SoC	711	6.51	-	-	-
Nirmatrelvir/ritonavir	1950	6.51	Dominated	-1239	-1239
Scenario 3 (baseline rates from previous high-risk analyses, efficacy data from **COVID-NMA** and starting ages of 70 and 65 for hospitalised and non-hospitalised patients)					
SoC	1053	9.97	-	-	-
Nirmatrelvir/ritonavir	1817	10.07	7827	1188	2164

ICERs ranging from below £20000 per QALY gained to dominated (no QALY gains in scenario 2).

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ICER, Incremental cost effectiveness ratio; QALY, Quality adjusted life years; NMB, Net monetary benefit; SoC, Standard care

Back-up slides

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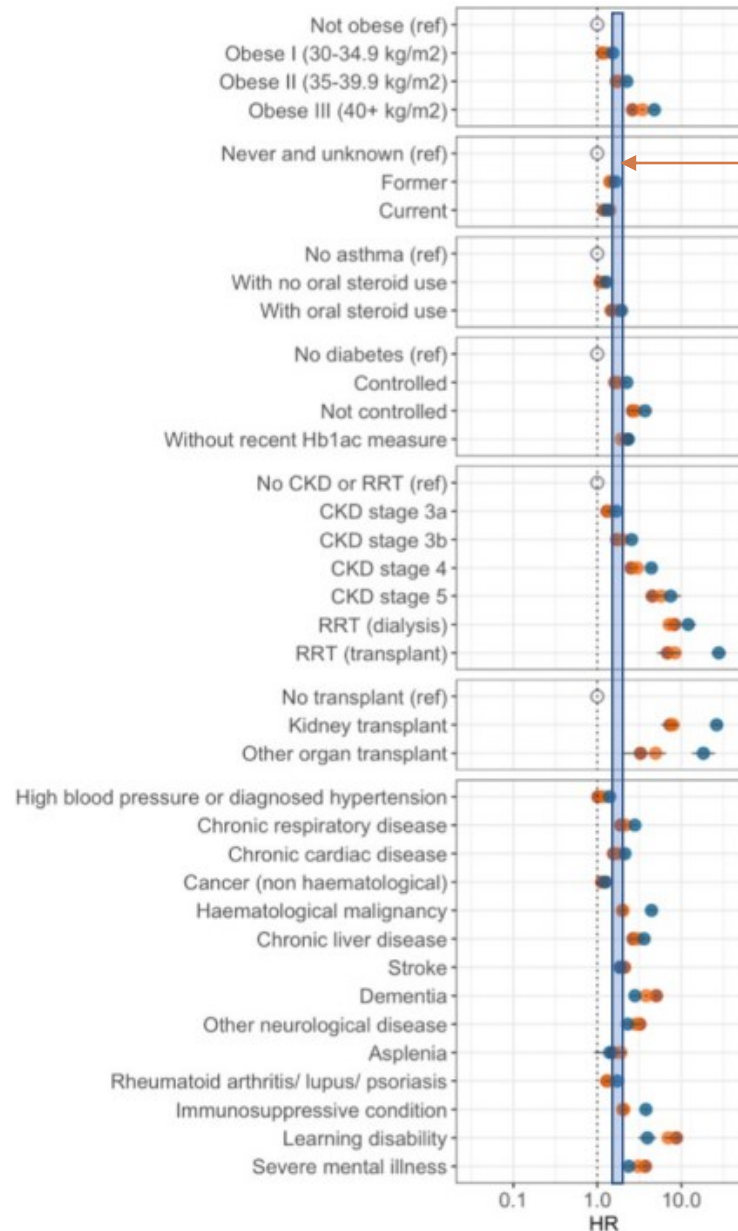# OpenSAFELY adapted figure from Edmunds report (1/2)
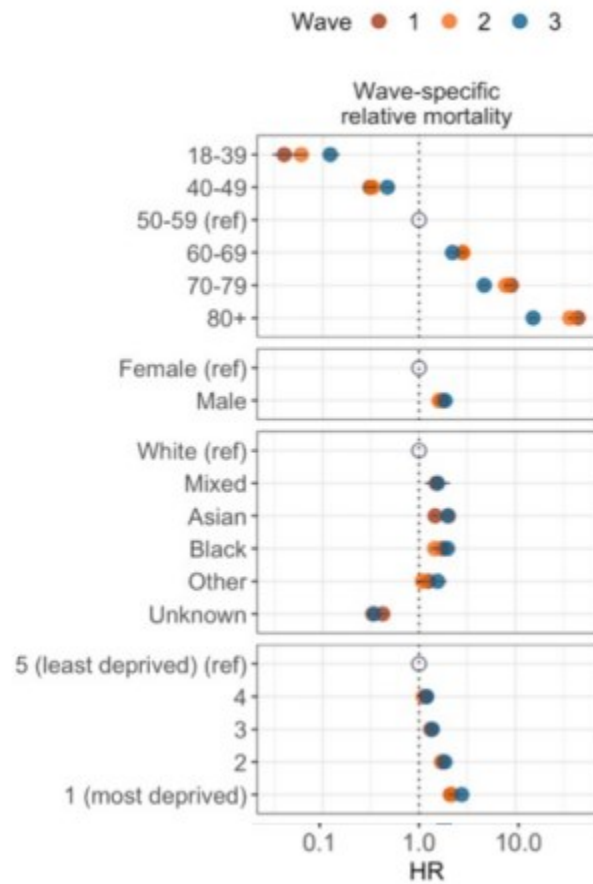
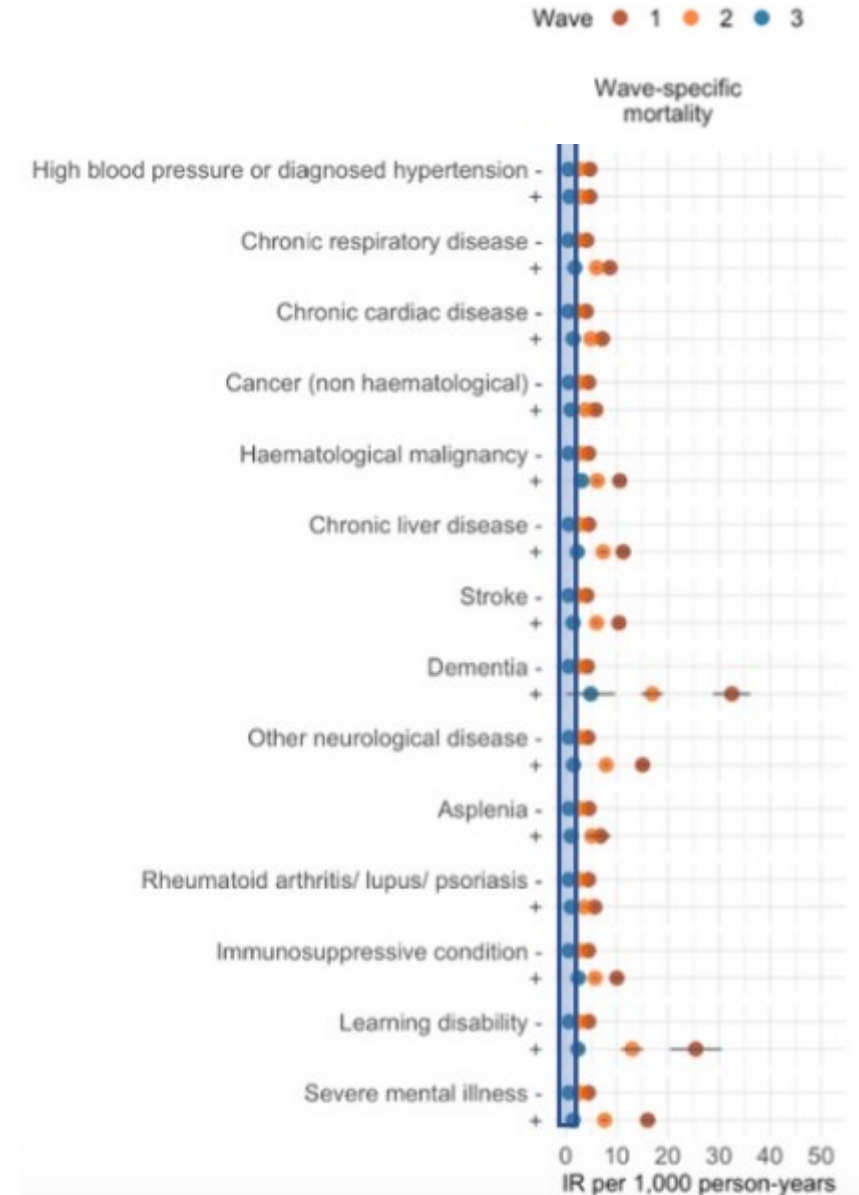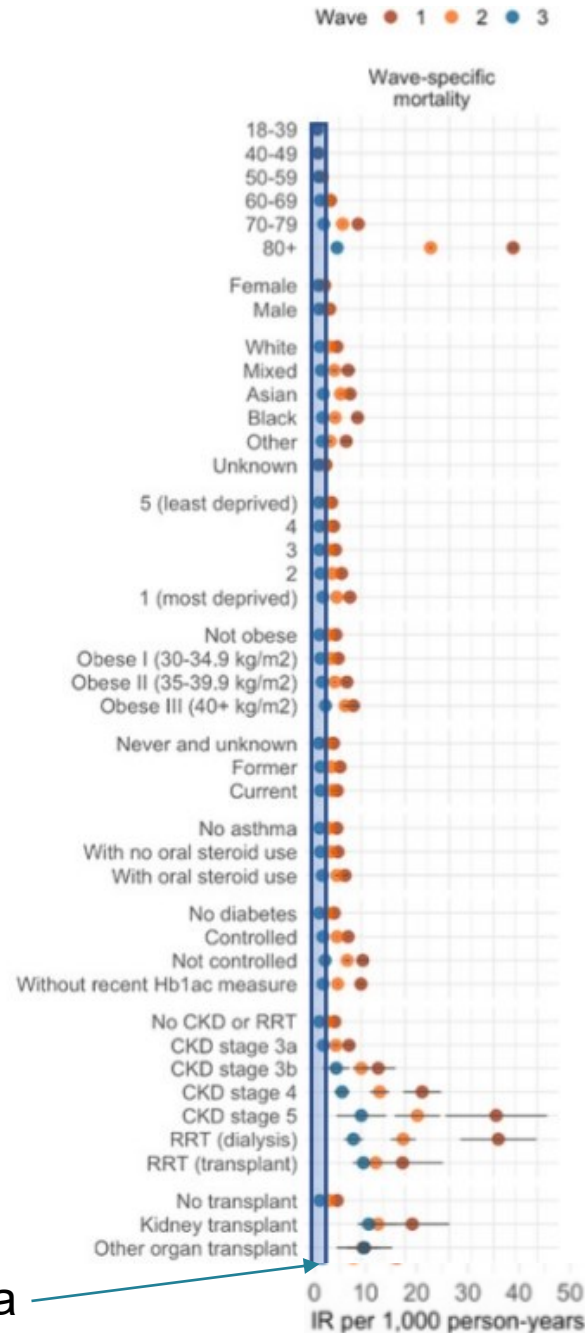Figure: OpenSAFELY Hazard ratio of death by demographic and socio-economic variables

The 95% CI on the hazard for rheumatoid arthritis, lupus and psoriasis
In the third wave is highlighted with a blue shaded bar

Figure: OpenSAFELY Hazard ratio of death by clinical conditions

OpenSAFELY adapted figure from Edmunds report (2/2)

Figure: Sex- and age-standardised COVID-19-related death rates (IR) and 95% confidence intervals per 1,000 person-years in OpenSAFELY in the three pandemic waves. Models were standardised for age and sex using the European standard population except for the death rates by age group (not standardised) and death rates by sex (standardised by age).
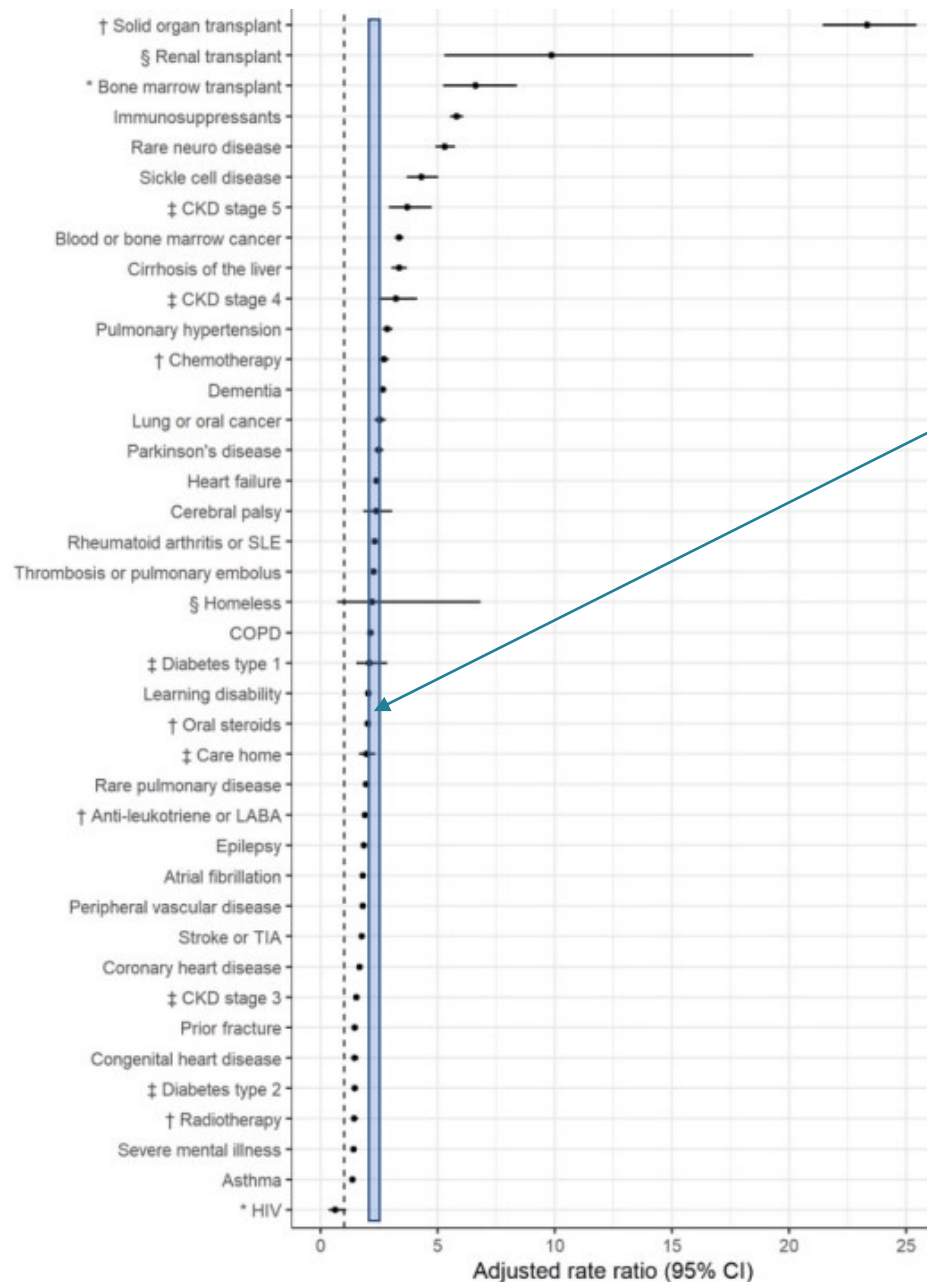
The 95% CI on the hazard for rheumatoid arthritis, lupus and psoriasis
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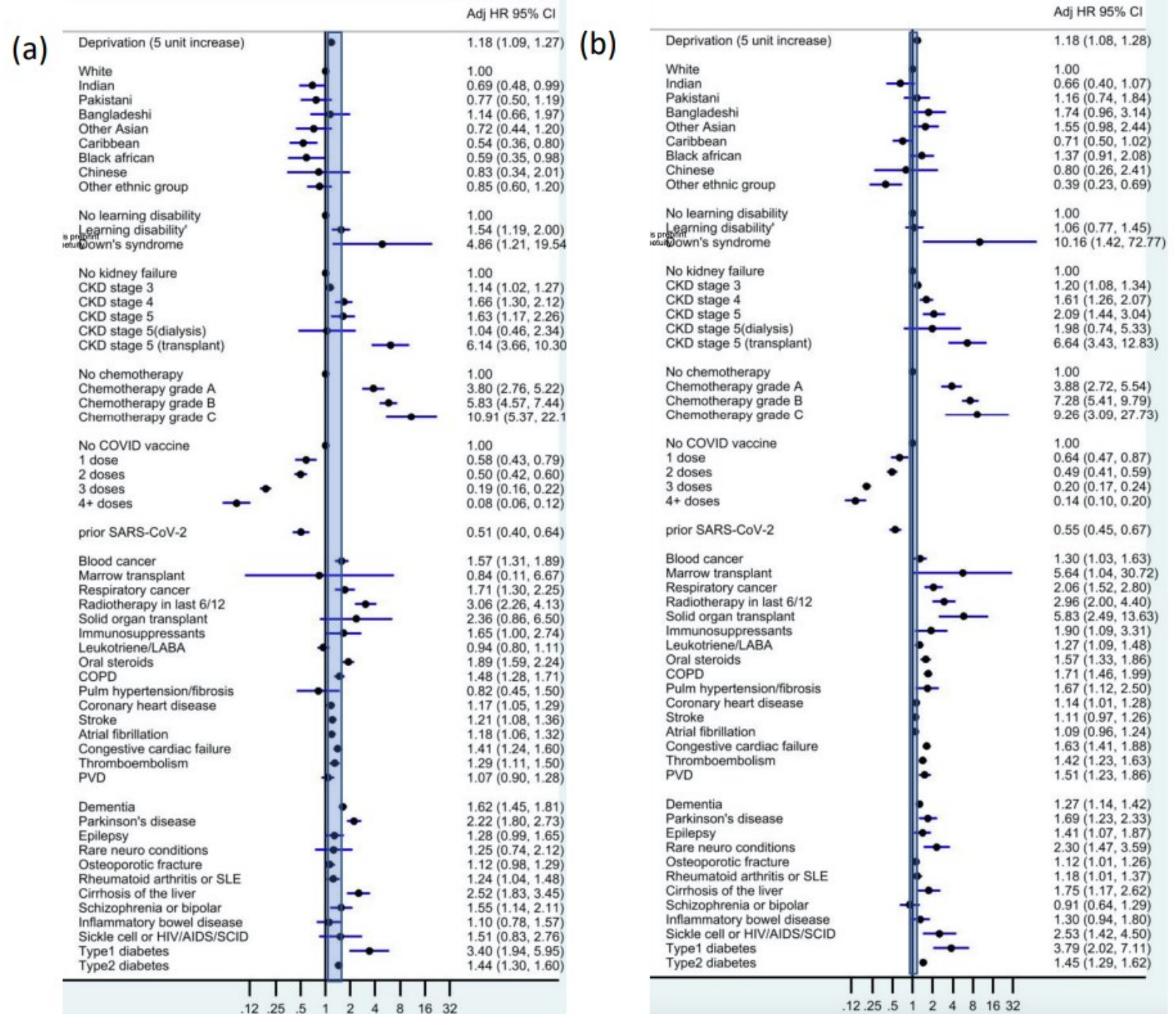
Agrawal adapted figure from Edmunds report

The 95% CI for the risk ratio associated with rheumatoid arthritis or SLE

Figure: Adjusted rate ratios (95% confidence intervals) for specific clinical risk factors associated with COVID-19 hospitalisation or death, among individuals who received booster doses MRNA-1273 or BNT162b2
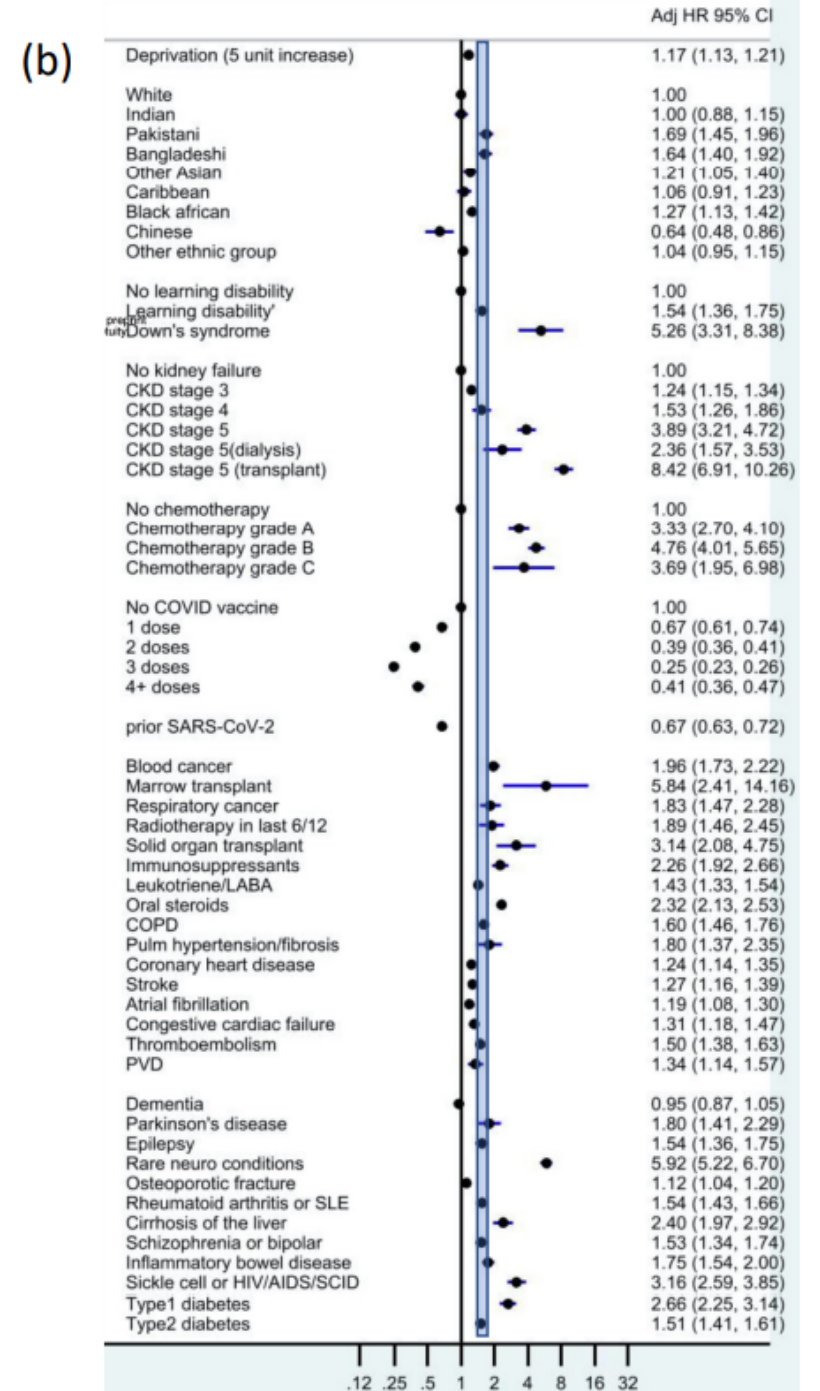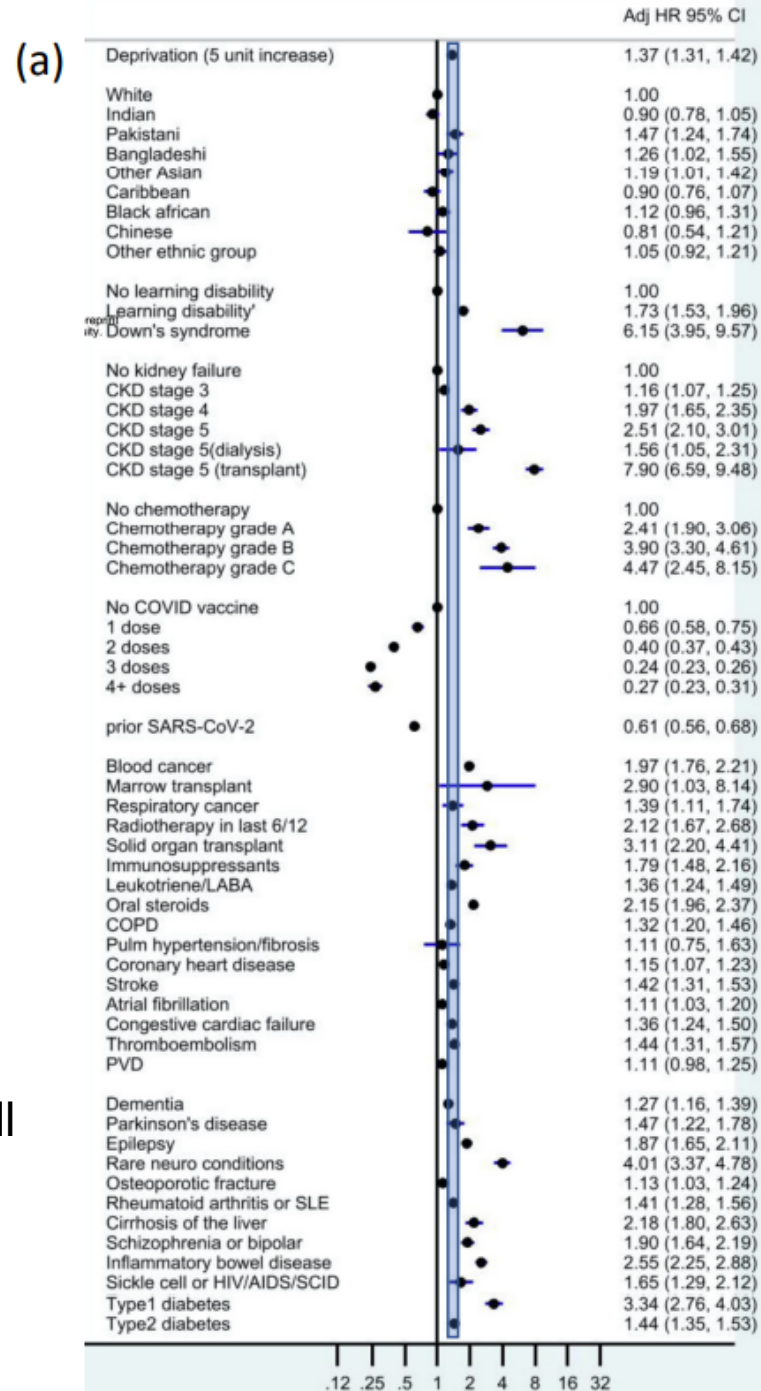
NICE

Hippisley-Cox adapted figure from Edmunds report (1/2)

Figure: Adjusted hazard ratio of deaths by clinical risk groups for males (a) and females (b). Adjustment for all variables including age and BMI.
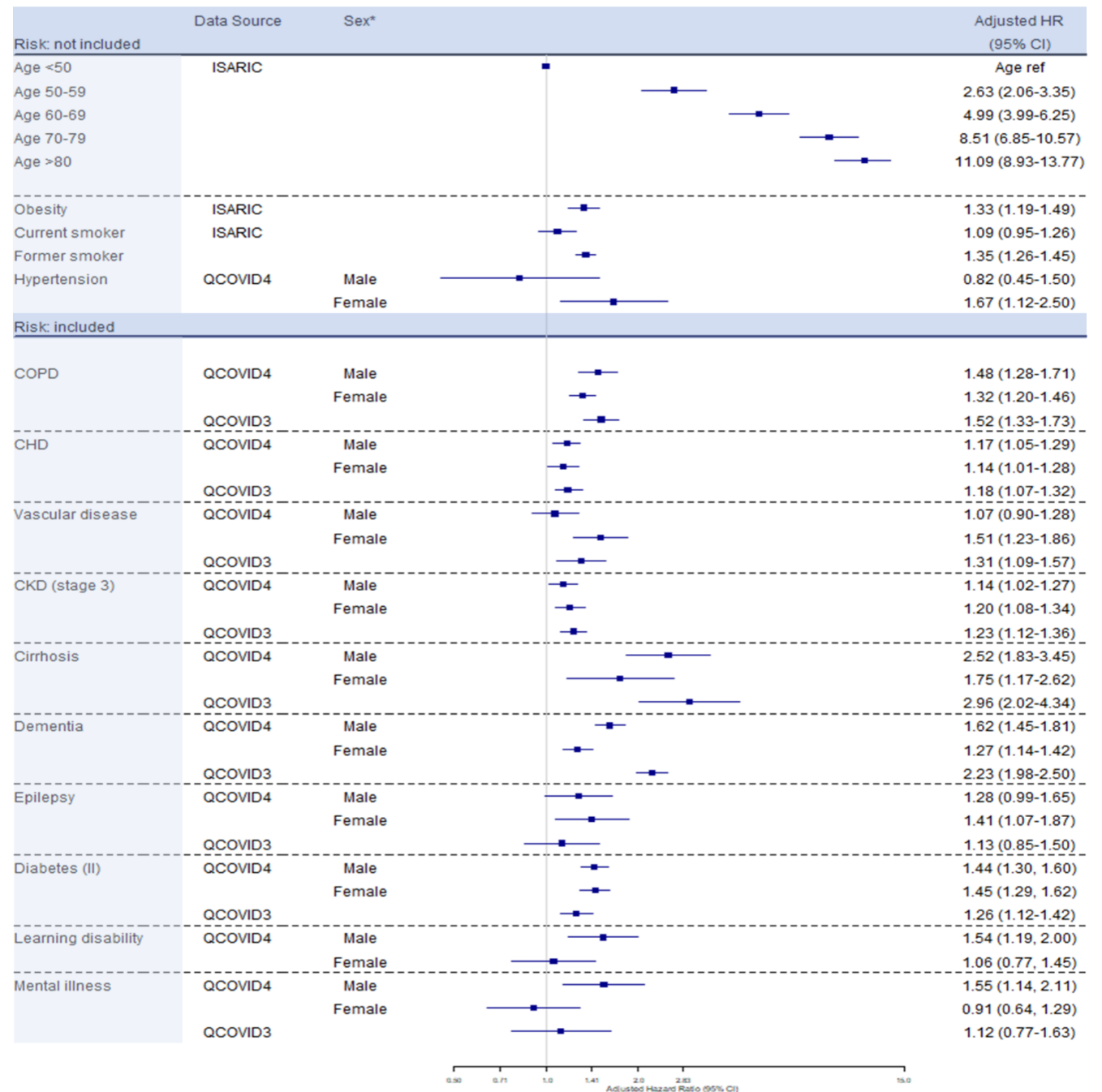
NICE

Hippisley-Cox adapted figure from Edmunds report (2/2)

Figure: Adjusted hazard ratio of hospitalisation by clinical risk groups for males (a) and females (b). Adjustment for all variables including age and BMI.

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Risk of death due to COVID-19 in at-risk populations (Figure created using data from QCOVID and ISARIC studies).
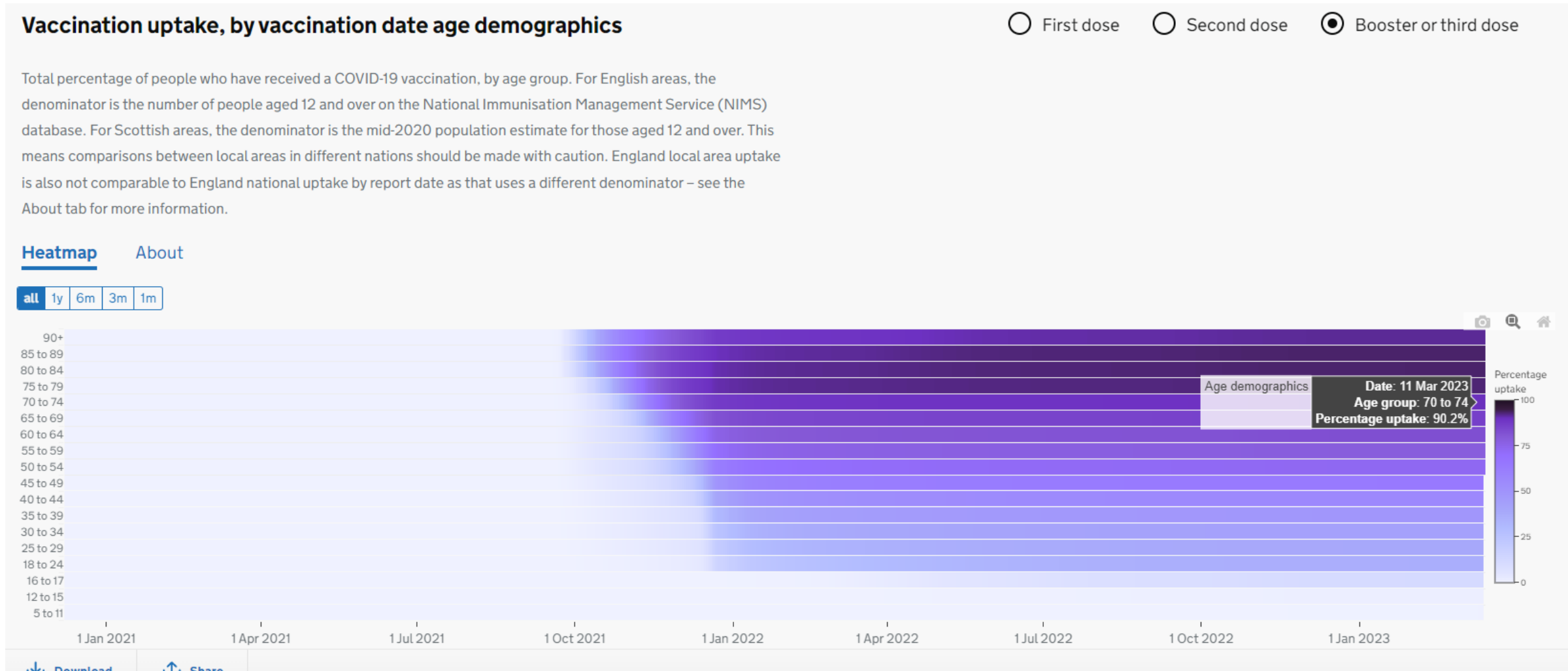
Sources:

https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland

MYE1: Population estimates: Summary for the UK, mid-2021

This worksheet contains one table.

Please choose from the links presented in the cells below to e-mail us your opinion on this table:

This met my needs, please produce it next year

I need something slightly different (please specify)

This is not what I need at all (please specify)

Groups/codes	United Kingdom	Great Britain	England and Wales	England	Wales	Scotland	Northern Ireland
Country Code	K02000001	K03000001	K04000001	E92000001	W92000004	S92000003	N92000002
All Persons	67,026,292	65,121,729	59,641,829	56,536,419	3,105,410	5,479,900	1,904,563
Females	34,214,835	33,247,086	30,439,748	28,854,074	1,585,674	2,807,338	967,749
Males	32,811,457	31,874,643	29,202,081	27,682,345	1,519,736	2,672,562	936,814
Age Groups	No data	No data	No data	No data	No data	No data	No data
0 to 4	3,580,269	3,467,237	3,211,800	3,058,217	153,583	255,437	113,032
5 to 9	3,933,947	3,809,411	3,515,684	3,340,262	175,422	293,727	124,536
10 to 14	4,034,833	3,907,703	3,603,137	3,419,970	183,167	304,566	127,130
15 to 19	3,794,214	3,680,436	3,396,806	3,222,056	174,750	283,630	113,778
20 to 24	4,034,799	3,924,493	3,592,515	3,407,413	185,102	331,978	110,306
25 to 29	4,367,126	4,251,185	3,880,467	3,694,908	185,559	370,718	115,941
30 to 34	4,655,236	4,529,805	4,146,472	3,950,366	196,106	383,333	125,431
35 to 39	4,477,368	4,349,739	3,989,765	3,802,908	186,857	359,974	127,629
40 to 44	4,226,466	4,103,925	3,771,374	3,595,148	176,226	332,551	122,541
45 to 49	4,214,569	4,093,631	3,755,333	3,571,818	183,515	338,298	120,938
50 to 54	4,640,482	4,509,869	4,120,078	3,904,317	215,761	389,791	130,613
55 to 59	4,573,856	4,444,320	4,042,910	3,819,992	222,918	401,410	129,536
60 to 64	3,956,096	3,842,169	3,481,543	3,280,891	200,652	360,626	113,927
65 to 69	3,354,034	3,260,087	2,954,663	2,776,651	178,012	305,424	93,947
70 to 74	3,345,116	3,261,381	2,971,227	2,790,122	181,105	290,154	83,735
75 to 79	2,490,287	2,423,025	2,218,726	2,084,906	133,820	204,299	67,262
80 to 84	1,698,442	1,654,382	1,511,707	1,422,689	89,018	142,675	44,060
85 to 89	1,050,295	1,023,973	937,985	884,349	53,636	85,988	26,322
90 and over	598,857	584,958	539,637	509,436	30,201	45,321	13,899
			70+ total	7,691,502			

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70-74 booster dose uptake rate March 2023 = 90.2%

Source: https://coronavirus.data.gov.uk/details/vaccinations?areaType=nation&areaName=England

NICE National Institute for
Health and Care Excellence

Thank you.