

Post-publications supplement to Williamson, E.J., Walker, A.J., Bhaskaran, K. *et al.* OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature* (2020). <https://doi.org/10.1038/s41586-020-2521-4>

NOT PEER REVIEWED

Background and purpose: In the above paper, working on behalf of NHS England, we estimated associations between a wide range of individual-level factors including demographics and comorbidities, and risk of COVID-19 death, but we did not explore interactions between variables. It is plausible that associations may depend on age, and evaluating this would inform more accurate risk prediction. The purpose of this supplement is therefore to present associations between individual-level factors and COVID-19 death, stratified by age group.

Methodology: We analysed the same dataset used to generate the original study results. This included the primary care records of 17,278,392 adults pseudonymously linked to 10,926 COVID-19-related deaths. Two sets of supplementary models were fitted:

- (i) Restricting those aged <70 years at 1st February 2020 (approximately the “working age” population): Within this sub-population we reproduced the analyses that generated Table 2 in the main paper. First, age- and sex- adjusted Cox models for each factor were fitted; then, we generated estimates mutually adjusted for all covariates.
- (ii) Age interaction models: In the full, unrestricted study population, we fitted a series of age-interaction models. For each covariate, we added an interaction with age group to the fully adjusted model, one by one (so that each model included just one age-covariate interaction). Age-stratified estimates of association were produced from the main effect and interaction terms, and a Wald p-value for interaction was calculated.

Results: Associations between covariates and COVID-19 death, estimated among those aged <70 years only are shown in Table 1. Age-stratified associations between covariates and COVID-19 death, for all age groups, are shown in Table 2. Associations of most covariates with COVID-19 death were larger in younger age groups, with strong evidence of interaction.

Interpretation: Younger age is known to be associated with a smaller absolute risk of COVID-19 death, but the relative importance of several other individual-level factors appears larger in younger age groups. This should be taken into account in risk prediction modelling.

Table 1. Hazard Ratios (HRs) and 95% confidence intervals (CI) for COVID-19 death among those age <70 years at 1st February 2020

Characteristic	Category	COVID-19 Death HR (95% CI)	
		Age-sex adj	Fully adj
Age	18-<40	0.05 (0.04-0.07)	0.08 (0.06-0.11)
	40-<50	0.27 (0.22-0.32)	0.37 (0.31-0.44)
	50-<60	1.00 (ref)	1.00 (ref)
	60-<70	2.83 (2.55-3.14)	1.85 (1.66-2.06)
Sex	Female	1.00 (ref)	1.00 (ref)
	Male	1.97 (1.78-2.17)	1.90 (1.71-2.10)
BMI	Not obese	1.00 (ref)	1.00 (ref)
	30-34.9kg/m2 (Obese class I)	1.59 (1.42-1.79)	1.17 (1.04-1.32)
	35-39.9kg/m2 (Obese class II)	3.04 (2.65-3.48)	1.84 (1.60-2.12)
	≥40 kg/m2 (Obese class III)	4.45 (3.79-5.23)	2.27 (1.92-2.69)
Smoking	Never	1.00 (ref)	1.00 (ref)
	Former	1.41 (1.28-1.56)	1.05 (0.95-1.17)
	Current	0.86 (0.74-1.00)	0.62 (0.53-0.73)
Ethnicity*	White	1.00 (ref)	1.00 (ref)
	Mixed	1.74 (1.11-2.72)	1.47 (0.94-2.29)
	South Asian	2.54 (2.18-2.97)	1.85 (1.57-2.18)
	Black	3.25 (2.64-4.01)	2.25 (1.81-2.79)
	Other	1.82 (1.33-2.50)	1.82 (1.32-2.50)
IMD quintile	1 (least deprived)	1.00 (ref)	1.00 (ref)
	2	1.15 (0.96-1.38)	1.08 (0.90-1.29)
	3	1.45 (1.22-1.72)	1.24 (1.05-1.48)
	4	2.29 (1.95-2.69)	1.80 (1.53-2.11)
	5 (most deprived)	2.89 (2.46-3.39)	2.05 (1.74-2.41)
Blood pressure	Normal	1.00 (ref)	1.00 (ref)
	High bp or diagnosed hypertension	1.87 (1.70-2.07)	1.21 (1.09-1.34)
Respiratory disease ex asthma		3.13 (2.75-3.56)	2.22 (1.93-2.55)
Asthma (vs none)**	With no recent OCS use	1.27 (1.11-1.45)	1.02 (0.89-1.17)
	With recent OCS use	2.40 (1.91-3.02)	1.33 (1.05-1.69)
Chronic heart disease		2.80 (2.49-3.14)	1.39 (1.23-1.58)
Diabetes (vs none)***	With HbA1c<58 mmol/mol	3.16 (2.79-3.57)	1.96 (1.73-2.23)
	With HbA1c≥58 mmol/mol	5.37 (4.73-6.09)	2.94 (2.56-3.37)
	With no recent HbA1c measure	3.09 (2.40-3.98)	1.96 (1.52-2.53)
Cancer (non-haematological, vs none)	Diagnosed < 1 year ago	4.62 (3.50-6.09)	3.83 (2.90-5.05)
	Diagnosed 1-4.9 years ago	2.16 (1.70-2.76)	1.85 (1.45-2.35)
	Diagnosed ≥5 years ago	1.45 (1.16-1.82)	1.32 (1.06-1.66)
Haematological malignancy (vs none)	Diagnosed < 1 year ago	9.59 (5.30-17.36)	6.64 (3.66-12.04)
	Diagnosed 1-4.9 years ago	7.76 (5.37-11.21)	5.81 (4.02-8.40)
	Diagnosed ≥5 years ago	2.67 (1.74-4.11)	2.02 (1.31-3.12)
Reduced kidney function (vs none)****	Estimated GFR 30-60	3.60 (3.11-4.17)	2.19 (1.89-2.54)
	Estimated GFR <30	23.06 (18.90-28.14)	7.87 (6.33-9.78)
Liver disease		4.02 (3.17-5.10)	2.15 (1.68-2.74)
Stroke/dementia		4.30 (3.66-5.05)	1.96 (1.65-2.33)
Other neurological disease		6.39 (5.32-7.69)	4.75 (3.92-5.75)
Organ transplant		11.98 (8.91-16.11)	2.33 (1.69-3.22)
Asplenia		2.70 (1.49-4.88)	1.67 (0.92-3.03)
Rheumatoid/Lupus/ Psoriasis		1.46 (1.24-1.71)	1.22 (1.04-1.44)
Other immunosuppressive condition		4.42 (3.04-6.42)	2.97 (2.04-4.32)

Models adjusted for age using a 4-knot cubic spline age spline, except for estimation of age group hazard ratios. *Ethnicity hazard ratios estimated from a model restricted to those with recorded ethnicity. **OCS = oral corticosteroids. Recent OCS use defined as in the year before baseline. ***HbA1c classification based on latest measure within 15 months before baseline. ****GFR = glomerular filtration rate in ml/min/1.73m², based on most recent serum creatinine measure

Table 2: Age-stratified associations between covariates and COVID-19 death, from interaction models

		Age-stratified HR and 95% CI (based on age in years, at 1 st February 2020)						P-value (age interaction)
		18-39 ⁺	40-49 ⁺	50-59	60-69	70-79	80 ⁺	
Sex	Female	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	<0.001
	Male	1.10 (0.68, 1.78)	1.65 (1.27, 2.16)	2.11 (1.84, 2.41)	1.81 (1.66, 1.98)	1.60 (1.51, 1.71)	1.52 (1.45, 1.60)	<0.001
BMI (vs not obese)	30-34.9kg/m2 (Obese class I)	1.83 (0.84, 4.00)	1.16 (0.72, 1.85)	1.67 (1.37, 2.03)	1.22 (1.07, 1.39)	1.14 (1.04, 1.24)	0.92 (0.86, 0.99)	<0.001
	35-39.9kg/m2 (Obese class II)	5.72 (2.84, 11.50)	2.89 (1.80, 4.63)	2.79 (2.22, 3.51)	1.98 (1.68, 2.32)	1.26 (1.11, 1.45)	1.13 (1.00, 1.28)	
	≥40 kg/m2 (Obese class III)	9.83 (4.89, 19.80)	5.05 (3.11, 8.18)	3.49 (2.64, 4.62)	2.52 (2.05, 3.10)	1.72 (1.43, 2.06)	1.29 (1.03, 1.60)	
Smoking (vs never-smoker)	Former	0.67 (0.36, 1.27)	0.87 (0.63, 1.20)	1.30 (1.11, 1.52)	1.28 (1.16, 1.41)	1.21 (1.13, 1.29)	1.19 (1.13, 1.25)	<0.001
	Current	0.29 (0.12, 0.72)	0.48 (0.30, 0.77)	0.73 (0.58, 0.94)	0.79 (0.66, 0.95)	0.93 (0.81, 1.07)	1.08 (0.95, 1.24)	
Ethnicity*	White	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	<0.001
	Mixed	1.39 (0.19, 10.10)	4.14 (1.94, 8.83)	2.55 (1.36, 4.76)	0.35 (0.09, 1.41)	1.74 (1.08, 2.80)	1.22 (0.82, 1.80)	
	South Asian	2.86 (1.57, 5.23)	1.80 (1.16, 2.79)	2.41 (1.84, 3.16)	2.39 (2.01, 2.85)	1.69 (1.43, 1.99)	0.95 (0.83, 1.10)	
	Black	3.59 (1.42, 9.08)	2.30 (1.25, 4.23)	3.86 (2.90, 5.14)	2.36 (1.74, 3.22)	1.43 (1.06, 1.92)	0.96 (0.78, 1.18)	
	Other	2.20 (0.68, 7.13)	0.94 (0.30, 2.95)	2.12 (1.22, 3.67)	2.01 (1.33, 3.04)	0.85 (0.53, 1.37)	1.30 (0.99, 1.72)	
IMD quintile	1 (least deprived)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	<0.001
	2	0.53 (0.16, 1.80)	0.81 (0.44, 1.48)	1.35 (1.04, 1.74)	1.04 (0.88, 1.23)	1.07 (0.96, 1.19)	1.15 (1.07, 1.24)	
	3	1.56 (0.72, 3.39)	1.71 (1.09, 2.69)	1.37 (1.06, 1.77)	1.23 (1.05, 1.44)	1.30 (1.17, 1.43)	1.18 (1.10, 1.27)	
	4	2.52 (1.32, 4.83)	2.26 (1.50, 3.39)	2.42 (1.96, 2.98)	1.82 (1.59, 2.09)	1.47 (1.33, 1.62)	1.42 (1.32, 1.53)	
	5 (most deprived)	2.25 (1.15, 4.39)	2.68 (1.82, 3.95)	2.72 (2.22, 3.33)	2.14 (1.88, 2.45)	1.91 (1.73, 2.10)	1.62 (1.50, 1.75)	
Blood pressure (vs normal)	High bp or diagnosed hypertension	2.39 (1.35, 4.22)	2.31 (1.75, 3.05)	1.80 (1.58, 2.06)	1.07 (0.98, 1.17)	0.84 (0.79, 0.89)	0.78 (0.74, 0.82)	<0.001
Respiratory disease ex asthma		3.65 (0.51, 26.21)	5.40 (3.04, 9.62)	3.56 (2.77, 4.58)	2.13 (1.84, 2.46)	1.87 (1.72, 2.03)	1.42 (1.34, 1.51)	<0.001
Asthma (vs none)**	With no recent OCS use	1.12 (0.57, 2.19)	1.07 (0.69, 1.65)	1.33 (1.06, 1.67)	1.06 (0.89, 1.25)	1.01 (0.90, 1.14)	0.94 (0.86, 1.02)	<0.001
	With recent OCS use	1.55 (0.22, 11.18)	3.12 (1.54, 6.29)	2.79 (1.94, 4.01)	1.17 (0.85, 1.62)	1.20 (0.99, 1.47)	0.94 (0.80, 1.10)	<0.001
Chronic heart disease		6.48 (2.05, 20.50)	3.84 (2.25, 6.56)	3.01 (2.44, 3.71)	1.64 (1.44, 1.86)	1.32 (1.23, 1.42)	1.03 (0.98, 1.08)	<0.001
Diabetes (vs none)***	With HbA1c<58 mmol/mol	7.15 (2.63, 19.44)	5.66 (3.74, 8.55)	3.46 (2.81, 4.26)	1.96 (1.72, 2.23)	1.44 (1.33, 1.57)	1.09 (1.03, 1.16)	<0.001
	With HbA1c≥58 mmol/mol	10.60 (3.89, 28.86)	7.70 (4.92, 12.05)	5.17 (4.15, 6.42)	3.24 (2.81, 3.74)	2.10 (1.88, 2.34)	1.48 (1.35, 1.62)	
	With no recent HbA1c measure	2.98 (0.41, 21.38)	4.79 (2.26, 10.17)	4.13 (2.79, 6.10)	1.76 (1.24, 2.51)	2.32 (1.91, 2.81)	1.64 (1.45, 1.86)	
Cancer (non-haematological, vs none)*	Diagnosed < 1 year ago	20.42 (9.11, 45.79)		2.06 (0.77, 5.49)	3.96 (2.92, 5.38)	2.00 (1.59, 2.51)	1.19 (0.97, 1.46)	<0.001
	Diagnosed 1-4.9 years ago	8.05 (3.81, 17.03)		2.58 (1.55, 4.30)	1.62 (1.22, 2.16)	1.21 (1.02, 1.43)	1.00 (0.88, 1.14)	
Haematological malignancy* (vs none)	Diagnosed ≥5 years ago	4.75 (2.25, 10.05)		1.88 (1.18, 3.00)	1.09 (0.83, 1.42)	0.92 (0.81, 1.05)	0.94 (0.87, 1.01)	
	Diagnosed < 1 year ago	24.55 (3.45, 174.85)		8.57 (2.14, 34.31)	7.61 (3.80, 15.24)	3.20 (1.89, 5.40)	1.87 (1.17, 2.96)	<0.001
	Diagnosed 1-4.9 years ago	15.80 (3.93, 63.44)		16.76 (9.49, 29.59)	4.48 (2.70, 7.45)	3.70 (2.80, 4.89)	1.32 (0.97, 1.79)	
	Diagnosed ≥5 years ago	6.94 (2.23, 21.65)		2.91 (1.21, 7.00)	1.94 (1.12, 3.34)	1.75 (1.32, 2.34)	1.46 (1.21, 1.77)	
Reduced kidney function (vs none)****	Estimated GFR 30-60	32.13 (10.19, 101.36)	8.17 (4.04, 16.50)	4.48 (3.33, 6.04)	2.18 (1.86, 2.56)	1.35 (1.25, 1.46)	1.20 (1.14, 1.26)	<0.001
	Estimated GFR <30	114.97 (41.96, 315.02)	21.27 (8.73, 51.81)	24.39 (17.34, 34.30)	8.59 (6.63, 11.12)	4.49 (3.86, 5.22)	1.83 (1.67, 2.01)	
Liver disease		16.29 (5.17, 51.33)	2.66 (0.85, 8.30)	3.70 (2.40, 5.70)	2.36 (1.75, 3.19)	1.51 (1.16, 1.98)	1.34 (1.02, 1.74)	<0.001
Stroke/dementia*		4.93 (2.20, 11.07)		4.42 (3.21, 6.08)	2.70 (2.26, 3.24)	2.52 (2.30, 2.76)	1.99 (1.89, 2.11)	<0.001

Other neurological disease	7.66 (1.88, 31.14)	15.54 (9.40, 25.68)	5.84 (4.04, 8.45)	4.17 (3.32, 5.25)	3.43 (2.99, 3.92)	1.89 (1.69, 2.12)	<0.001
Organ transplant*	9.11 (3.40, 24.46)		6.70 (3.79, 11.86)	5.66 (3.91, 8.20)	2.33 (1.44, 3.76)	1.45 (0.69, 3.04)	<0.001
Asplenia*	3.01 (0.42, 21.40)		1.54 (0.39, 6.18)	2.23 (1.12, 4.47)	0.91 (0.46, 1.83)	1.32 (0.86, 2.03)	0.42
Rheumatoid/Lupus/ Psoriasis	2.15 (0.79, 5.85)	1.39 (0.74, 2.60)	1.51 (1.11, 2.05)	1.23 (1.01, 1.50)	1.25 (1.11, 1.41)	1.12 (1.02, 1.23)	0.27
Other immunosuppressive condition	33.36 (13.56, 82.07)	4.00 (1.28, 12.46)	4.04 (2.17, 7.53)	2.61 (1.40, 4.85)	1.63 (0.90, 2.94)	1.36 (0.79, 2.34)	<0.001

*youngest age categories combined for some variables due to small numbers of events. Models adjusted for age using a 4-knot cubic spline age spline, plus an interaction between age group and covariate. Each age interaction was estimated in a separate model. *Ethnicity hazard ratios estimated from a model restricted to those with recorded ethnicity. **OCS = oral corticosteroids. Recent OCS use defined as in the year before baseline. ***HbA1c classification based on latest measure within 15 months before baseline. ****GFR = glomerular filtration rate in ml/min/1.73m², based on most recent serum creatinine measure