Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research paper

The impact of primary care supported shielding on the risk of mortality in people vulnerable to COVID-19: English sentinel network matched cohort study

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SUMMARY

Objectives: To mitigate risk of mortality from coronavirus 2019 infection (COVID-19), the UK government recommended 'shielding' of vulnerable people through self-isolation for 12 weeks.
Methods: A retrospective cohort study using a nationally representative English primary care database comparing people aged >= 40 years who were recorded as being advised to shield using a fixed ratio of 1:1, matching to people with the same diagnoses not advised to shield ($n = 77{,}360$ per group). Time-to-death was compared using Cox regression, reporting the hazard ratio (HR) of mortality between groups. A sensitivity analysis compared exact matched cohorts ($n = 24{,}752$ shielded, $n = 61{,}566$ exact matches).
Results: We found a time-varying HR of mortality between groups. In the first 21 days, the mortality risk in people shielding was half those not (HR = 0.50, 95%CI:0.41–0.59. $p < 0.0001$). Over the remaining nine weeks, mortality risk was 54% higher in the shielded group (HR=1.54, 95%CI:1.41–1.70, $p < 0.0001$). Beyond the shielding period, mortality risk was over two-and-a-half times higher in the shielded group (HR=2.61, 95%CI:2.38–2.87, $p < 0.0001$).
Conclusions: Shielding halved the risk of mortality for 21 days. Mortality risk became higher across the remainder of the shielding period, rising to two-and-a-half times greater post-shielding. Shielding may be beneficial in the next wave of COVID-19.

Introduction

In England, COVID-19-related excess mortality largely occurred between weeks 12 to 22 of the year 2020 and primarily affected people age 45 years and older (Fig. 1).[1–4] Insufficient protection for care home staff and residents,[5–7] exacerbation of existing health inequalities[8,9] and missed diagnoses of common conditions including cancer, particularly haematological malignancies and cardiovascular disease,[10] may all have exacerbated mortality alongside the large number of COVID-19-related deaths.[11–14] Effective clinical interventions include the finding that corticosteroids may play a role in alleviating the implicated pathologic inflammatory response, reducing mortality in critically ill patients.[15,16] Mitigating actions for infection prevention included advising those deemed extremely likely to be vulnerable to COVID-19 to self-isolate, termed 'shielding,' for 12 weeks. [17]

Shielding, and the need to protect the vulnerable was initially announced on 12th March and subsequently implemented across the NHS as a three-step process. Firstly, national datasets were searched to identify individuals at 'high risk,' of developing complications following COVID-19 infection, based on criteria agreed by the UK's Chief Medical Officers. Secondly, primary care data were

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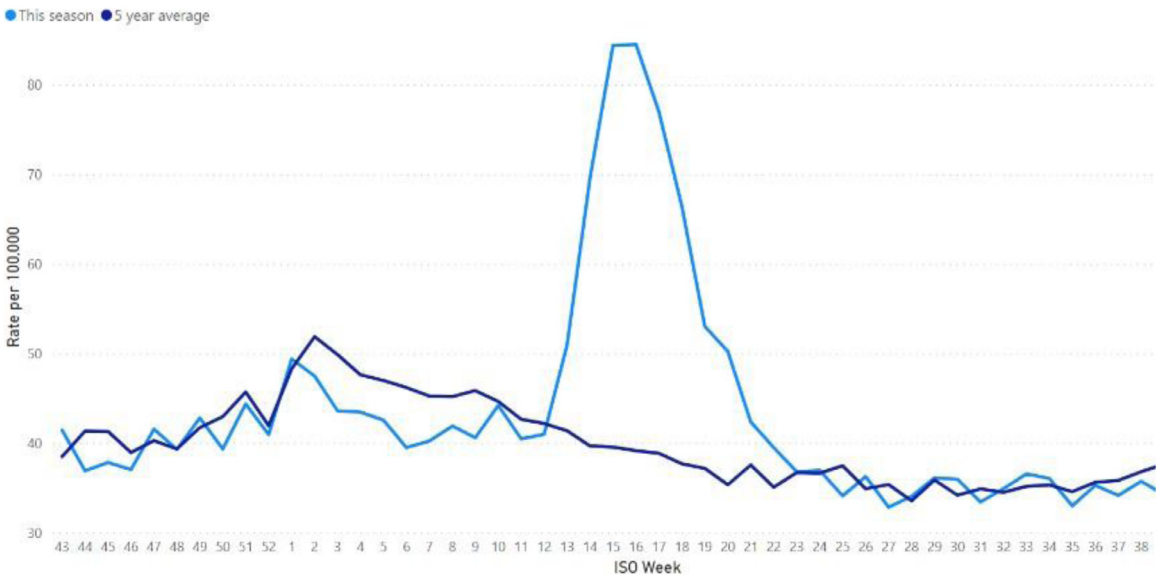

Fig. 1. Mortality in people aged ≥ 45 years old per 100,000 of the English primary care sentinel network population by international standards organisation (ISO) week, comparing this year's death rate with that for the previous five years. The peak in mortality, weeks 12 to 22, coincides with the first wave of the COVID9 pandemic[18].

searched centrally (data are held by NHS Digital) using these clinical criteria, and the people identified sent a letter advising them they were on the Shielded Patient List (SPL).[19] This process was not without problems, with some patients having died and others not considering themselves vulnerable.[19] General practitioners (GPs) then added and subtracted patients from this list of people at 'high risk'. GPs then contacted their patients to confirm or add them to the 'high risk' category, or to let them know they were reclassified as 'medium' or 'low' risk. Template letters were provided to support this process. GPs coded into computerised medical records (CMR) those they considered 'high risk'. The first letter to GPs was on 21st March, with a follow-up on 3rd April, with a request this work was completed by 14th April, all dates well within COVID-19′s first wave mortality peak (these dates correspond to International Standards Organisation (ISO) weeks 12, 14 and 16, Fig. 1).

We carried out this study to test whether recommending those at 'high risk' to shield may have been effective and reduced mortality. We analysed whether people in the 'high risk' category, aged 40 years or older, receiving shielding advice reinforced by their GP, reduced the risk of mortality compared with a matched cohort of people not advised to shield.

Method

Study design

Our primary analysis was a matched cohort study to compare the risk of mortality in those who were at 'high risk' and advised to shield compared with those who were not, using propensity-matched controls. We also conducted a sensitivity analysis using an exact matched cohort. Our outcome measure was hazard ratio (HR) of mortality between the two groups using Cox's proportional hazards model, adjusted for baseline covariates.

We constructed three mutually exclusive follow-up periods, estimating distinct hazard ratios for the shielding effect in each follow-up period, because we found the hazard of mortality changed over time. We divide the 12-week shielding period into the first three weeks (0–21days), and subsequent nine weeks (22–84 days), then the remainder of our period of observation.

Data for the study were extracted between International Standards Organisation (ISO) Weeks 12–39 (16/3/2020–27/9/2020), giving a maximum observation period of 195 days depending on the date GPs contacted their patent with shielding advice. We report the study according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidance.

Population and settings

We included people aged 40 years old and above, registered with general practices who are part of the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), a nationally representative population ($N = 3{,}994{,}125$). Our exposed group were people flagged as 'high risk' of COVID-19 and needing to shield for 12 weeks. We started our observation period from 16th March 2020. People were included from the date when the 'high risk' code was recorded in their CMR. Patients entered the cohort on the index date when the shielding code was first added to their electronic health record, with matched controls added from the same date.

Study variables

Our primary outcome was all-cause mortality during the study period. We measured time-to-event from the date a 'high risk' term was included in a patient's record until death, the study observational period ends (195 days) or the participant is censored, in this study de-registered from their general practice. Our primary variable of interest is if people were flagged as 'high risk' of COVID-19 complications and recommended to shield.

Variables for analysis included a wide range of demographic and clinical risk groups thought to impact on COVID-19.

We included the following sociodemographic variables: sex, age, ethnicity divided into Asian, White, and Black, Mixed and Other, using an ontology to maximise case identification,[20] household size as determined based upon a pseudonymised household key derived from identical addresses, practice-level urban-rural status as derived from Lower Layer Super Output Area (LSOA, a geographical subunit with a minimum population of 1,000), socioeconomic status using the Index of Multiple Deprivation (IMD) quintiles (we combined the two most deprived quintiles as there

are almost no lowest quintile people in rural areas), body mass index (BMI) using World Health Organisation categorisation of overweight (25–29Kg/m^2), obese (BMI 30–34Kg/m^2) and severely obese (BMI $\geq$ 35Kg/m^2), and smoking status divided into current, ex-smokers and non-smokers. We also added possible surrogate markers of complexity care. These included recording if individuals were care home residents, if the patient has a care plan (patient-held summaries of health and care needs, generally provided to people with more complex needs), or polypharmacy, where we divided prescriptions into 1–2, 3–4, or 5 or more different long-term medications. We defined polypharmacy as 5 or more.

We included the following clinical risk groups as they may have been associated with an increased mortality rate: hypertension, chronic kidney disease (CKD) defined as stages 3–5, rheumatoid arthritis, heart disease (including acute myocardial infarction, atrial fibrillation and congestive cardiac failure), stroke (haemorrhagic and ischaemic), haematological malignancy (including Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukaemia, myeloma), learning disability and an immunocompromised state (excluding malignancy) due to taking medication for inflammatory conditions, chronic respiratory disease (including asthma) and chronic obstructive pulmonary disease (COPD). We included the use of steroid inhalers in the last 6 months and use of inhaled bronchodilators in the last 6 months as steroids may impact on disease progression.

Comparator

Each patient advised to shield was matched to a non-shielded patient in a 1:1 fixed ratio. People were matched on the basis of propensity scores[21,22] and on the following exact matching variables: sex, age (banded), ethnicity (banded), house size (banded), asthma diagnosis and history of inhaler use in the 6 months prior to the study start date (both steroid inhalers and inhaled bronchodilators). The propensity score used the exact matching baseline variables listed above plus the following study variables: smoking status, care home status, history of a care plan in the two years prior to the study start date.

Outcomes

We report unadjusted rates of survival comparing the unshielded ($n = 1348{,}354$), and shielded ($n = 97,963$). We report HRs in our matched cohort between shielded people and propensity-matched controls, reporting separate HRs for any periods where there was a marked difference in risk.

Statistical methods

Propensity scores (the likelihood of being given a code for shielding) were estimated using logistic regression. We fitted the propensity score model by using baseline characteristics at the individual start date for all patients, the date their 'high risk' code was recorded in their record. To mitigate effects of immortal time bias, study entry date of unshielded individuals coincided with their shielded counterpart. Matching was based on both exact matching variables and distance within a calliper (setting a calliper width at 0.2 of the standard deviation of the logit of the propensity score).[21,22] We used descriptive statistics to characterise the study cohort (Table 1). Differences were quantified using standardised mean differences (SMD), with a score under 0.1 indicating good balance. Crude mortality incidence rates with 95% confidence intervals were calculated.

To generate hazard ratios, we used Cox's proportional hazards model, adjusted for baseline covariates, fitting two models: the base model and an adjusted model. The base model included the shielding status indicator variable only. The adjusted model included exact matching variables, all variables used in the propensity score, and, in a sensitivity analysis, groups based on quintiles of propensity scores. We tested the proportional hazards assumption for the adjusted survival model and we accommodated deviation from the proportional hazards assumption by fitting piecewise constant coefficients for the shielding status in three contiguous follow up periods evaluated posthoc. Epochs that were derived identified time periods where there were non-time-varying effects. The follow-up period was divided in 84 days (to account for the 12-week recommended shielding period) and beyond 84 days. Iterative halving of these two sets of follow-up periods till the proportional hazards assumption was not violated led to the three epochs of: 0–21 days, 22–84 days, and greater than 84 days.

We carried out a sensitivity analysis fitting a survival model to an exact matched cohort comparing people recommended to shield ($n = 24{,}752$) and those not ($n = 61{,}566$).

We also report the crude mortality in the people GPs regarded from high to moderate or low risk (see also Supplementary Materials).

Ethical approval

The RCGP RSC's work concerning SARS-CoV-2 has been approved by Public Health England's Caldicott Guardian Committee as fitting under Regulation 3 of the Health Service Control Patient Information Regulations 2002. The study was approved by RCGP.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation nor writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 1,446,317 patients aged 40 years or more in the RCGP RSC population fully registered on 16th March 2020. Of these 97,963 (6.77%) were recommended to shield. A propensity-matched cohort was created for 77,360 of these patients; the shielded and non-shielded groups were well matched at baseline (Table 1).

We describe the time from the recommendation to shield being made to patients being contacted by their GP. We report overall unadjusted and adjusted mortality rates, then how the risk of mortality varied with time, and which elements of the model appeared to be associated with mortality.

Exposure to the recommendation to shield

The first shielding letter was issued to GPs on Saturday 21st March 2020. Following the start of implementation from 22nd March 2020, many patients were notified directly of the need to shield. This was augmented by GPs notifying patients who needed to shield and coding they had done so. A quarter of patients were notified by their GP within 4 days of receiving this request, half in 24 days and 75% within 30 days (Fig. 2). The mean duration was 26.5 days. The target date for completion was Tuesday 14th April (day 24) and half were completed by then. Half of these recommendations to shield would have been received before the pandemic peaked (week 16, 1319th April), and three-quarters before the excess peak in mortality was over (Figs. 1 and 2).

Table 1
Distribution of propensity score matching variables for matched cohorts within RCGP RSC cohort, sociodemographic and clinical covariates.

Variable	Category	Shielded	Percentage (%)	Not Shielded	Percentage (%)
Socio-demographic variables:					
Sample size		77,360		77,360	
Sex	Female	41,675	(53.9)	41,675	(53.9)
	Male	35,685	(46.1)	35,685	(46.1)
Age Band	40–64	30,375	(39.3)	30,375	(39.3)
	65–74	19,993	(25.8)	19,993	(25.8)
	75+	26,992	(34.9)	26,992	(34.9)
Ethnicity	White	69,824	(90.3)	69,824	(90.3)
	Asian	3,813	(4.9)	3,813	(4.9)
	Black/Mixed/Other	3,723	(4.8)	3,723	(4.8)
IMD quintile	1,2	28,440	(36.8)	28,440	(36.8)
	3	15,405	(19.9)	15,405	(19.9)
	4	16,031	(20.7)	16,031	(20.7)
	5	17,484	(22.6)	17,484	(22.6)
Household dwelling size	1	26,032	(33.7)	26,032	(33.7)
	2–4	45,760	(59.2)	45,760	(59.2)
	5–8	3,964	(5.1)	3,964	(5.1)
	9+	1,604	(2.1)	1,604	(2.1)
Urban Rural Indicator	Rural	13,783	(17.8)	13,783	(17.8)
	Urban	63,577	(82.2)	63,577	(82.2)
BMI band	Normal weight	25,942	(33.5)	23,869	(30.9)
	Overweight	26,853	(34.7)	27,797	(35.9)
	Obese	20,669	(26.7)	21,958	(28.4)
	Severely obese	3,896	(5.0)	3,736	(4.8)
Smoking Status	Active Smoker	11,568	(15.0)	11,590	(15.0)
	Ex-smoker	48,202	(62.3)	48,395	(62.6)
	Non-smoker	17,590	(22.7)	17,375	(22.5)
Care Home Residency Status	No	76,121	(98.4)	76,113	(98.4)
	Yes	1,239	(1.6)	1,247	(1.6)
Care Plan within last 2 years	No	72,952	(94.3)	72,929	(94.3)
	Yes	4,408	(5.7)	4,431	(5.7)
Polypharmacy	1–2	6,527	(8.4)	6,298	(8.1)
	3–4	7,229	(9.3)	7,414	(9.6)
	5 or more	63,604	(82.2)	63,648	(82.3)
Variable	**Category**	**Shielded**	**Percentage (%)**	**Not Shielded**	**Percentage (%)**
Clinical covariates:					
Hypertension	No	36,092	(46.7)	36,106	(46.7)
	Yes	41,268	(53.3)	41,254	(53.3)
Chronic Kidney Disease (Stages 3–5)	No	62,366	(80.6)	62,708	(81.1)
	Yes	14,994	(19.4)	14,652	(18.9)
Rheumatoid Arthritis	No	72,128	(93.2)	72,128	(93.2)
	Yes	5,232	(6.8)	5,232	(6.8)
Heart disease					
Acute Myocardial Infarction	No	72,061	(93.2)	71,705	(92.7)
	Yes	5,299	(6.8)	5,655	(7.3)
Atrial Fibrillation	No	67,763	(87.6)	68,071	(88.0)
	Yes	9,597	(12.4)	9,289	(12.0)
Congestive Cardiac Failure	No	70,595	(91.3)	70,698	(91.4)
	Yes	6,765	(8.7)	6,662	(8.6)
Stroke					
Haemorrhagic Stroke	No	76,420	(98.8)	76,367	(98.7)
	Yes	940	(1.2)	993	(1.3)
Ischaemic Stroke	No	76,059	(98.3)	75,958	(98.2)
	Yes	1,301	(1.7)	1,402	(1.8)
Chronic Respiratory Disease					
Asthma Diagnosis	No	55,887	(72.2)	55,887	(72.2)
	Yes	21,473	(27.8)	21,473	(27.8)
COPD Diagnosis	No	62,132	(80.3)	61,676	(79.7)
	Yes	15,228	(19.7)	15,684	(20.3)
Chronic Lung Disease	No	65,801	(85.1)	65,136	(84.2)
	Yes	11,559	(14.9)	12,224	(15.8)
Inhaled Bronchodilators	No	55,646	(71.9)	56,672	(73.3)
in last 6 months	Yes	21,714	(28.1)	20,688	(26.7)
Steroid Inhalers in last 6 months	No	58,276	(75.3)	59,436	(76.8)
	Yes	19,084	(24.7)	17,924	(23.2)
Malignancy					
Hodgkin's Lymphoma	No	77,348	(100.0)	77,350	(100.0)
	Yes	12	(0.0)	10	(0.0)
Non-Hodgkin's Lymphoma	No	77,196	(99.8)	77,230	(99.8)
	Yes	164	(0.2)	130	(0.2)
Leukaemia	No	77,252	(99.9)	77,302	(99.9)
	Yes	108	(0.1)	58	(0.1)
Myeloma	No	77,312	(99.9)	77,331	(100.0)
	Yes	48	(0.1)	29	(0.0)
Immunocompromised	No	74,972	(96.9)	75,279	(97.3)
	Yes	2,388	(3.1)	2,081	(2.7)
Learning Disability	No	76,725	(99.2)	76,628	(99.1)
	Yes	635	(0.8)	732	(0.9)

Table 2
Crude all-cause mortality rate with (95% CI). Numbers surviving and deceased up until the end of the follow-up period of the study.

Not recommended to shield		'High risk' from COVID-19 shielding recommended	
Surviving	Deaths	Surviving	Deaths
1,338,755	9,599	94,160	3,803
133 (131,136) per 10,00 person years		730 (700,750) per 10,000 person years	

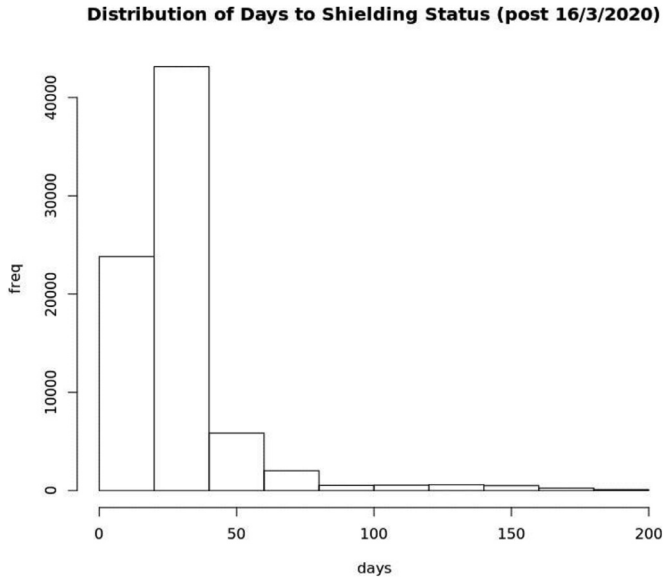

Fig. 2. Distribution of days to shielding recommendations being sent to 'high risk' people to shield, baseline 16th March 2020 (ISO week 12; the start of data extraction period), median 24 days (25th centile 4 days, 75th centile 30 days), mean 26.5 days.

Mortality risk associated with shielding status

Our unadjusted analysis showed people at 'high risk' from COVID-19, who were recommended to shield had an overall increased risk of all-cause mortality (HR 2.13 95% CI 1.95–2.33; $p < 0.0001$, Table 2). After adjustment, people recommended to shield still had higher all-cause mortality than those not recommended (HR=1.70, 95%CI: 1.60–1.80, $p < 0.0001$, Table 3B).

Time-varying effect of shielding on mortality

While overall recommendation to shield is associated with increased all-cause mortality across the whole study period, there was considerable variation over time (Fig. 3).

In the first 21 days following GP recommendation to shield, there was a halving of the risk of mortality compared to the matched control population (HR=0.4952, $p < 0.0001$). However, the risk of all-cause mortality increased in the remaining nine weeks of proposed shielding, rising to one-and-a-half times that of the control population (HR=1.5449 , $p < 0.0001$). After the shielding period ended, mortality in the shielding group was substantially higher, over two-and-a half times that of controls (HR= 2.6143, $p < 0.0001$, Table 3A).

We report the association of individual variables with mortality as these may inform which variables to include in any future shielding intervention (Table 3B).

Across sociodemographic factors, male gender, age, deprivation (where the most deprived two quintiles were at greater risk), living alone or in large (including likely communal) dwellings, and polypharmacy were associated with greater risk. The greatest risks were age 75-years and older (HR = 3.17, 95%CI2.86–3.50, $p < 0.0001$), households of 9 or more, which is likely to include residential homes (HR = 2.74, 95%CI:2.38–3.15, $p < 0.0001$) and polypharmacy (HR = 2.63, 95%CI:2.13–3.24, $p < 0.0001$). Asian ethnicity and obesity were associated with lower risk (Table 3B).

Cardiovascular disease, CKD, atrial fibrillation and heart failure were associated with greater risk; whereas this was not the case for hypertension and people who have had myocardial infarctions. People who have had a haemorrhagic stroke were at greater risk, whereas those with ischaemic strokes were not.

Asthma diagnosis was associated with lower risk, whereas COPD was associated with an increased risk of mortality. Interestingly those prescribed an inhaled bronchodilator were at increased risk of mortality (HR = 1.1748, 95%CI:1.0734–1.2858, $p < 0.001$), whereas those prescribed a steroid inhaler had a lower risk of mortality (HR=0.880, 95%CI:0.798–0.971, $p = 0.011$).

Among haematological malignancies, people diagnosed with Hodgkin's lymphoma were at particularly high risk (HR = 12.24, 95%CI:4.58–32.67, $p < 0.0001$), though the confidence interval is wide. There was also increased risk in other lymphoma's but not demonstrated for leukaemia or myeloma.

People who risk being immunocompromised, outside of those with malignancies, were not at increased risk.

The sensitivity analysis, a complete cases survival analysis, reported similar findings. The people who GPs regraded to moderate or low risk had a similar mortality to those not advised to shield (Supplementary Materials).

Discussion

Principal findings

Recommendation to shield was associated with a short-term effect in reducing the risk of mortality in the shielded population, compared with matched controls. However, the protective effect lasted less than twelve weeks. At the end of the shielding period, mortality HR for the shielded group rose to more than two-and-a-half times that of the matched group. Additionally, we have associations with increased mortality, which may help improve the design of any future interventions.

Implications

Shielding may provide a short-term decrease in the risk of mortality, but the intervention as delivered across the first wave of the pandemic may be insufficient. However, it is impossible to know whether this group would have had a different relative risk had they not been shielded; or if the matched controls might have benefitted more.

GPs' assessment of the greater risk of mortality appears to have face validity; notwithstanding these cohorts were matched for sociodemographic factors and clinical conditions, the individuals picked out for shielding overall had a greater risk of mortality. Similarly, those GPs reclassified as medium or low risk had a similar unadjusted mortality to those not advised to shield (Supplementary Materials). Given the negative consequences of shielding (on physical and mental health, not accessing vital medical care, etc.), policymakers should carefully consider the extent to which

Table 3
(A) Base Model Hazard ratios for base survival models of matched cohort.

	Hazard ratio (HR)	**Lower 95% confidence interval**	**Upper 95% confidence interval**	**Probability** *p*
Shielding Status follow-up 0–21 days	0.4952	0.4144	0.5918	< 0.0001
Shielding Status follow-up 22-84 days	1.5449	1.408	1.6952	< 0.0001
Shielding Status follow-up 85–195 days	2.6143	2.3831	2.868	< 0.0001

(B) Fully adjusted model Hazard ratios for fully adjusted survival models of matched cohort.

	Hazard ratio (HR)	**Lower 95% confidence interval**	**Upper 95% confidence interval**	**Probability** *p*
Shielding Category (ref No)	1.6980	1.6000	1.8020	< 0.0001
Shielding Status follow-up 0–21 days	0.4918	0.4116	0.5878	< 0.0001
Shielding Status follow-up 22–84 days	1.5243	1.389	1.6727	< 0.0001
Shielding Status follow-up 85–195 days	2.587	2.3579	2.8383	< 0.0001
Sex (ref level: female)	1.3670	1.2866	1.4524	< 0.0001
Age Band (ref level 40–64)				
65–74	1.8311	1.6470	2.0358	< 0.0001
75+	3.1662	2.8636	3.5008	< 0.0001
Ethnicity (ref level White)				
Asian	0.7003	0.5895	0.8320	< 0.0001
Black/Mixed/Other	0.8494	0.7092	1.0172	0.0760
Deprivation Status (Quintiles)				
(ref *Q1&2 most deprived*)				
Q3	0.8709	0.8017	0.9461	0.0011
Q4	0.8659	0.798	0.9397	0.0006
Q5 (least deprived)	0.8762	0.8086	0.9495	0.0013
Household Dwelling Size (ref level one individual)				
2–4	0.8889	0.8325	0.9491	0.0004
5–8	1.4356	1.2351	1.6686	< 0.0001
9 or more individuals	2.7377	2.3814	3.1474	< 0.0001
Urban-Rural Practice (ref Level Rural)				
Urban	0.9911	0.9173	1.0708	0.8207
BMI Band (ref level Normal weight)				
Overweight	0.6847	0.6397	0.7328	< 0.0001
Obese	0.5904	0.5445	0.6402	< 0.0001
Severely Obese	0.7345	0.6214	0.8682	0.0003
Polypharmacy (ref level: 1 or 2 drugs)				
3,4 medications	1.2827	0.9941	1.6549	0.0556
5 or more medications	2.6265	2.1278	3.2421	< 0.0001
Clinical condition, reference: absence	**Hazard ratio** (HR)	**Lower 95% confidence interval**	**Upper 95% confidence interval**	**Probability** *p*
Hypertension	0.9332	0.8744	0.996	0.0375
Chronic Kidney Disease (Stages 3–5)	1.2741	1.1932	1.3606	< 0.0001
Heart disease				
Acute Myocardial Infarction	1.0594	0.9663	1.1615	0.2188
Atrial Fibrillation	1.2075	1.1220	1.2994	< 0.0001
Congestive Cardiac Failure	1.5792	1.4577	1.7109	< 0.0001
Stroke				
Haemorrhagic Stroke	1.3072	1.0869	1.5721	0.0044
Ischaemic Stroke	1.0418	0.8914	1.2175	0.6066
Chronic Respiratory Disease				
Asthma Diagnosis	0.7309	0.6698	0.7976	< 0.0001
COPD	1.1789	1.0480	1.3263	0.0061
Chronic Lung Disease	0.8730	0.7712	0.9883	0.0318
Inhaled Bronchodilators in last 6 months	1.1748	1.0734	1.2858	0.0005
Steroid Inhalers in last 6 months	0.8804	0.7982	0.9712	0.0109
Haematological Malignancy				
Hodgkin's Lymphoma	12.236	4.5836	32.6645	< 0.0001
Non-Hodgkin's Lymphoma	2.1391	1.2383	3.6951	0.0064
Leukaemia	1.3382	0.637	2.8113	0.4417
Myeloma	2.2025	0.915	5.3017	0.0781
Immunocompromised *(excluding malignancy)*	0.8255	0.6744	1.0105	0.0630
Rheumatoid Arthritis	0.6934	0.5974	0.8049	< 0.0001
Learning Disability	1.2309	0.9161	1.6539	0.1680

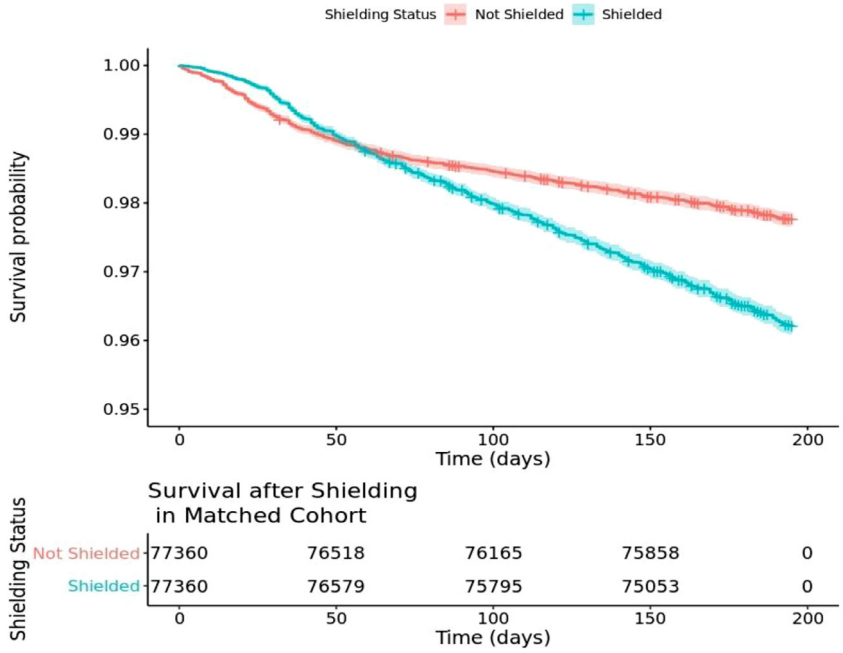

Fig. 3. Kaplan-Meier survival plot comparing the group recommended to shield ('Shielded' blue curve) with those not recommended to shield ('Not shielded' red curve). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

high risk patients should be asked to shield in future waves of the pandemic. It is possible that these results, combined with others could allow a more focussed approach.

Comparison with the literature

There is a dearth of analyses as to whether shielding should be part of our response to future waves of COVID-19. Segmentation of the population to enable shielding of the extremely clinically vulnerable individuals whilst the wider population returns to normalcy has been suggested.[21] It has also been proposed that shielding for 38 weeks alongside mask-wearing and social distancing may see up to 62% reduction in mortality.[22] Whilst lockdown is effective, it has immense socioeconomic impact and may exacerbate existing social inequalities,[1] and whilst local level responses are a nuanced alternative, how shielding might be incorporated is far from clear.[23] Those we identify at greatest risk might be more selectively shielded. Many of our findings are corroborated. There is other evidence suggesting that age is the overwhelmingly dominant factor for mortality risk (those $\geq$ 45 years old saw increased mortality risk of 20 – 35% compared to those $<$ 45, with 0–14% increased risk).[1, 24–27] We have previously reported the association of chronic disease with mortality, which has also been reported in other studies.[1,6,28,29] We reported the increased risk of mortality associated with care homes, which too has been found by other groups.[30] The association with living conditions has also been reported, given that transmission of infectious disease is assumed to be density-dependent.[31,32]

The effectiveness of shielding may be questioned when mortality in care home communities has been high.[31] There are important ethical considerations when shielding, with a balance required between the risk of disease transmission and the mental and cognitive health effects of isolation, particularly with the lack of visitors.[32,33]

The challenge is to develop specific and structured rationalised shielding policy that is relevant to an individual's circumstances which extends to their immediate support system and employers and is not jeopardised by financial or professional obstacles. Government guidance regarding shielding has been deemed vague and not behaviourally specific.[32] There must be consideration as to what extent shielding is realistic for those who cannot shield due to work and family commitments.[34] GPs have had a significant role in recommending shielding. NHS Digital reported at the end of the shielding period that 30.1% of the additional recommendations to shield have come from GPs. GPs have also deducted 14.7% of people from the 'high risk' list; suggesting a significant impact on the shaping of the list.[35]

Strengths and limitations

The strengths of this study include a large population size ($n = 1{,}446{,}317$) which has a large proportion of shielded individuals in the sample (6.77%), and that both the unadjusted and fully adjusted models yielded similar results.

Limitations include that routine clinical data does not contain much information about the variation in disease severity. The difference between the GP-nominated group to shield and the matched controls might be accounted for by disease severity. Whilst we looked to include surrogates for this, such as having a care plan and polypharmacy, the people who GPs recommended to shield had worse mortality of the latter period after the end of shielding.

The mean time from symptom onset to death in COVID-19 is 17.8 days.[34] It might be questioned whether there was time for shielding to work. However, with intention to recommend shielding announced by the government prior to commencement and with the delay prior to GPs contacting and coding high risk patients, GPs' action was reinforcement, as opposed to the only element, of the intervention. With a mean 26.5-day delay in time for shield coding addition, the meantime for symptom onset to death would have been accounted for.

The study of shielding classification does not imply full compliance with shielding guidelines. The analysis would have benefited from including an indicator of previous engagement in preventative healthcare. This would provide an approximate indication as to the likelihood of the patient to engage and comply with

shielding, as well as disease management, in partnership with their care team. Finally, whilst we appreciate that mortality risk for the shielded group was greater in the longer term, we feel that is unlikely that recommendation to shield resulted in this later greater risk of mortality. The greater mortality rate corresponds with the summer months where there was little community transmission, thus this may represent the overall greater risk of mortality of the shielded group, reflecting the validity of their GPs' clinical judgement.

Call for further research

Additional analyses should urgently examine whether there was a genuine early reduction in mortality and if the intervention were more intensive whether this would have a sustained effect. Behavioural research into how compliance can be enacted and maintained as well as psychological and economic research into how to maintain mental health and to execute shielding without inducing financial stress can be supportive towards implementing a more holistic course of action.

Conclusions

The initial three-week period of shielding following contact from their GP was associated with half the mortality risk compared with matched controls. After this period, any benefit disappeared, and the shielding group has a 50% higher risk of mortality. At the end of the 12-week shielding period, those asked to shield had an increased risk of mortality over two-and-a-half times more than controls, a constant difference they maintained across the summer. These data are challenging to interpret, but it is plausible that shielding had an initial very positive effect, that then partially wore off, followed by a reversion to a higher rate of mortality. The associations from this observational study should be urgently tested on another dataset, and the reinstatement of more targeted shielding should be considered in the emergent second wave of COVID-19.

Data sharing

The RCGP RSC data set can be accessed by researchers, approval is on a project-by-project basis (www.rcgp.org.uk/rsc). Ethical approval by an NHS Research Ethics Committee is needed before any data release/other appropriate approval. Researchers wishing to directly analyse the patient-level pseudonymised data will be required to complete information governance training and work on the data from the secure servers at the University of Surrey. Patient-level data cannot be taken out of the secure network. We encourage interested researchers to attend the short courses on how to analyse primary-care data/RCGP RSC data offered twice a year.

Declaration of Competing Interest

SdeL is the director of RCGP RSC. He has unrelated projects funded by GSK, Seqirus and has been a member of Global Advisory Boards for Seqirus and Sanofi. FDRH reports personal fees from Novartis and Boehringer Ingelheim and grants from Pfizer. All other authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.04.033.

References

[1]. Joy M, Hobbs FDR, McGagh D, Akinyemi O, de Lusignan S. Excess mortality from COVID-19 in an english sentinel network population. *Lancet Infect Dis* 2020. doi:10.1016/S1473-3099(20)30632-0.
[2]. de Lusignan S, Joy M, Oke J, et al. Disparities in the excess risk of mortality in the first wave of COVID-19: cross sectional study of the english sentinel network. *J Infect* 2020. doi:10.1016/j.jinf.2020.08.037.
[3]. Analysis of death registrations not involving coronavirus (COVID-19), England and Wales-office for national statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/

analysisofdeathregistrationsnotinvolvingcoronaviruscovid19englandandwales28december2019to1may2020/technicalannex (Accessed 6 October 2020).
[4]. Spiegelhalter D. Use of "normal" risk to improve understanding of dangers of COVID-19. *BMJ* 2020;**370**. doi:10.1136/bmj.m3259.
[5]. Lai CC, Wang JH, Ko WC, et al. COVID-19 in long-term care facilities: an upcoming threat that cannot be ignored. *J Microbiol Immunol Infect* 2020;**53**:444–6.
[6]. Burki T. England and Wales see 20,000 excess deaths in care homes. *Lancet* 2020;**395**:1602.
[7]. Daly M. COVID-19 and care homes in England: what happened and why? *Soc Policy Adm* 2020. doi:10.1111/spol.12645.
[8]. Bambra C, Riordan R, Ford J, Matthews F. The COVID-19 pandemic and health inequalities. *J Epidemiol Community Health* 2020;**74**:2020–214401 jech.
[9]. Coronini-Cronberg S, John Maile E, Majeed A. Health inequalities: the hidden cost of COVID-19 in NHS hospital trusts? *J R Soc Med* 2020;**113**:179–84.
[10]. Rubinstein SM, Warner JL. COVID-19 and haematological malignancy: navigating a narrow strait. *Lancet Haematolsss* 2020;**7**:e701–3.
[11]. Yekedüz E, Karcıoğlu AM, Utkan G, Ürün Y. A clinical dilemma amid COVID-19 pandemic: missed or encountered diagnosis of cancer? *Future Oncol* 2020;**16**:1879–81.
[12]. Williams R, Jenkins DA, Ashcroft DM, et al. Diagnosis of physical and mental health conditions in primary care during the COVID-19 pandemic: a retrospective cohort study. *Lancet Public Health* 2020;**0**:e543.
[13]. Rutter MD, Brookes M, Lee TJ, Rogers P, Sharp L. Impact of the COVID-19 pandemic on UK endoscopic activity and cancer detection: a national endoscopy database analysis. *Gut* 2020. doi:10.1136/gutjnl-2020-322179.
[14]. Earnshaw CH, Hunter HJA, McMullen E, Griffiths CEM, Warren RB. Reduction in skin cancer diagnosis, and overall cancer referrals, during the COVID-19 pandemic. *Br J Dermatol* 2020 published online June 4.. doi:10.1111/bjd.19267.
[15]. . Dexamethasone in hospitalized patients with COVID-19 -preliminary report. *N Engl J Med* 2020 published online July 17. doi:10.1056/nejmoa2021436.
[16]. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA J Am Med Assoc* 2020;**324**:E1–13.
[17]. Kmietowicz Z. COVID-19: highest risk patients are asked to stay at home for 12 weeks. *BMJ* 2020;**368**:m1170 Clinical research Ed..
[18]. COVID-19 | clininf.eu. https://clininf.eu/index.php/cov-19/(Accessed 17 October 2020).
[19]. Wise J. Covid-19: experts divide into two camps of action-shielding versus blanket policies. *BMJ* 2020;**370**:m3702 Clinical research ed.
[20]. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm. Stat.* 2011;**10**:150–61.
[21]. Hoertel N, Blachier M, Blanco C, et al. A stochastic agent-based model of the SARS-CoV-2 epidemic in France. *Nat Med* 2020;**26**:1417–21.
[22]. Smith GD, Spiegelhalter D. Shielding from covid-19 should be stratified by risk. *BMJ* 2020;**369**. doi:10.1136/bmj.m2063.
[23]. Turcanu V, Maleki SJ, Lack G. Characterization of lymphocyte responses to peanuts in normal children, peanut-allergic children, and allergic children who acquired tolerance to peanuts. *J Clin Investig* 2003;**111**:1065–72.
[24]. Barron E, Bakhai C, Kar P, et al. Associations of type 1 and type 2 diabetes with COVID-19 related mortality in England: a whole-population study. *Lancet Diabet Endocrinol* 2020;**8**:813–22.
[25]. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet* 2020;**395**:1907–18.
[26]. Deiana G, Azara A, Dettori M, et al. Deaths in SARS-CoV-2 positive patients in Italy: the influence of underlying health conditions on lethality. *Int J Environ Res Public Health* 2020;**17**:1–10.
[27]. Michelozzi P, de'Donato F, Scortichini M, et al. Mortality impacts of the coronavirus disease (COVID-19) outbreak by sex and age: rapid mortality surveillance system, Italy, 1 February to 18 April 2020. *Eurosurveillance* 2020;**25**. doi:10.2807/1560-7917.ES.2020.25.19.2000620.
[28]. Graham NSN, Junghans C, Downes R, et al. SARS-CoV-2 infection, clinical features and outcome of COVID-19 in United Kingdom nursing homes. *J Infect* 2020;**81**:411–19.
[29]. Li Y, Temkin-Greener H, Shan G, Cai X. COVID-19 Infections and deaths among connecticut nursing home residents: facility correlates. *J Am Geriatr Soc* 2020;**68**:1899–906.
[30]. House T, Keeling MJ. Household structure and infectious disease transmission. *Epidemiol Infect* 2009;**137**:654–61.
[31]. Identifying older people most vulnerable to COVID-19 | British geriatrics society. https://www.bgs.org.uk/resources/identifying-older-people-most-vulnerable-to-covid-19 (Accessed 4 October 2020).
[32]. Petersen I. Is stratified shielding from COVID-19 feasible and ethical? *BMJ* 2020;**370**. doi:10.1136/bmj.m2660.
[33]. Michie S, West R, Rogers MB, Bonell C, Rubin GJ, Amlôt R. Reducing SARS-CoV-2 transmission in the UK: a behavioural science approach to identifying options for increasing adherence to social distancing and shielding vulnerable people. *Br J Health Psychol* 2020. doi:10.1111/bjhp.12428.
[34]. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis* 2020;**20**:669–77.
[35]. Coronavirus shielded patient list open data set, England - NHS digital. https://digital.nhs.uk/dashboards/shielded-patient-list-open-data-set (Accessed 19 October 2020).