**Pre-pandemic Mental Health and COVID-19 Vaccine Hesitancy: Cohort Study**

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Contributions: GDB generated the idea for the present manuscript. DA built the dataset, conducted all analyses, and prepared the displayable items. All authors developed an analytical plan and commented on a manuscript drafted by GDB.

**Abstract**

*Background*: Whereas several predictors of COVID-19 vaccine hesitancy have been examined, the role of cognitive function following the widely publicised development of an inoculation is unknown.

*Objective*: To test the association between scores from an array of cognitive function tests and self-reported vaccine hesitancy after the announcement of the successful testing of the Oxford University/AstraZeneca vaccine.

*Design, Setting, and Participants*: We used individual-level data from a pandemic-focused study (COVID Survey), a prospective cohort study nested within Understanding Society (Main Survey). In the week immediately following the announcement of successful testing of the first efficacious inoculation (November/December 2020), data on vaccine intentionality were collected in 11740 individuals (6702 women) aged 16-95. Pre-pandemic scores on general cognitive function, ascertained from a battery of six tests, were captured in 2011/12 wave of the Main Survey.

*Measurements*: Self-reported intention to take up a vaccination for COVID-19. To summarise our results, we computed odds ratios with accompanying 95% confidence intervals for general cognitive function adjusted for selected covariates.

*Results*: Of the study sample, 17.2% (N=1842) indicated they were hesitant about having the vaccine. After adjustment for age, sex, and ethnicity, study members with a lower baseline cognition score were markedly more likely to be vaccine hesitant (odds ratio per standard deviation lower score in cognition; 95% confidence interval: 1.76; 1.62, 1.90). Adjustment for mental and physical health plus household shielding status had no impact on these results, whereas controlling for educational attainment led to partial attenuation but the probability of hesitancy was still elevated (1.52; 1.37, 1.67). There was a linear association for vaccine hesitancy across the full range of cognition scores (p for trend: p<0.0001).

*Limitations:* Our outcome was based on intention rather than behaviour.

*Conclusions*: Erroneous social media reports might have complicated personal decision-making, leading to people with lower cognitive ability test scores being vaccine-hesitant. With people with lower cognition also experiencing higher rates of COVID-19 in studies conducted prior to vaccine distribution, these new findings are suggestive of a potential additional disease burden.

**Introduction**

These observations provide circumstantial evidence for a link between cognitive ability and another health-protecting behaviour, vaccine uptake. Vaccination is central to controlling the present pandemic, with success reliant on a sufficiently high uptake to achieve herd immunity.1 In the only empirical investigation of which we are aware, investigators administered a very brief measure of analytical reasoning to people in two small cross-sectional studies from the UK (N=2025) and Ireland (N=1041).2 Relative to the group who indicated they would be likely to accept a COVID-19 inoculation if one became available, somewhat lower cognition scores were apparent in study members indicating vaccine reticence.2 These data were collected in March/April 2020 when no vaccine was available. Around 8 months later, following periodic statements to the media of its on-going development, successful testing of the Oxford University/AstraZeneca vaccine, the first known efficacious inoculation against COVID-19, was announced.3 Time-series analyses across multiple countries potentially implicates this declaration and those for other vaccines in having a positive impact upon intentionality.4 Accordingly, for the first time to our knowledge, we investigated the link between cognitive function and COVID-19 vaccine hesitancy in a large UK general population-based sample in which data collection took place following the announcement of an efficacious vaccine.

**Methods**

Understanding Society, also known as the UK Household Longitudinal Study, is a nationally-representative, on-going, open, cohort study (hereinafter, the ‘Main Survey’). Based on a clustered-stratified probability sample of households, participants have been interviewed annually since 2009.5 Households who had participated in at least one of the two most recent waves of data collection (wave 8, 2016-18; wave 9, 2017-19) comprised the target sample for a pandemic-focused study initiated in April 2020 (hereinafter, the ‘COVID Survey’).6,7 The derivation of the present analytical sample from the Main and COVID surveys, including the whereabouts of relevant data, is depicted in figure 1. The University of Essex Ethics Committee gave approval for data collection in the COVID-orientated surveys (ETH1920-1271); no further ethical permissions were required for the present analyses of anonymised data.

The COVID Surveys took place monthly/bimonthly between April (wave 1) and November 2020 (wave 6), with questions on vaccine intention first administered in the November wave when study members were aged 16-95 (mean 53).7 Data collection in wave 6 (starting 24th November) commenced the day immediately following the announcement of the efficacy of the Oxford University/AstraZeneca vaccine3 and continued for one week, comprising a total of 12,035 individuals of 19,294 invitations issued (response proportion, 62%).7

*Assessment of mental health*

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*Assessment of covariates*

In the third wave of data collection in the Main Survey (2011-2013), six cognitive function tests were administered following piloting.8,9 Representing a range of cognitive skills, these tests have been repeatedly deployed in large-scale, population-based studies.10-14 Verbal declarative memory was assessed using both *immediate word recall* and *delayed word recall* tasks. Respondents listened to a list of ten words delivered by a computer; they were then asked to immediately recall the words and, again, at a later stage in the interview without having heard the words again. The number of correct responses was recorded on each occasion. For *semantic verbal fluency*, respondents named as many animals as they could in one minute; the final score was based on the number of unique correct responses. Using components of screening instruments for *cognitive impairment* including the Mini Mental State Examination15 and the Cambridge Cognitive Examination,16 respondents were asked to subtract 7 from 100 and then subtract 7 from their answer on four more occasions. The number of correct responses of a maximum of five was recorded. *Fluid reasoning* was assessed using a number sequence in which the respondent populated the gap(s) in a logical series. Respondents were initially presented with simple examples to test their understanding; those who seemed confused or unable to understand test requirements after the relaying of two examples took no further part in the test. Remaining study members were administered two sets of three number sequences, with the difficulty of the second set determined by their performance on the first. A score was derived which accounts for the difficulty of the items. For *numerical reasoning skills*, individuals were given three numerical problems to solve and, depending on their responses, were then administered a further one (simpler) or two (more difficult) problems. The total number of correct responses was recorded.

Covariates were self-reported and included age; sex (both wave 10, Main Survey); ethnicity (wave 10, Main Survey; denoted as white or non-white); highest education level (wave 10, Main Survey; categorised as degree & other higher degree, A’ level or equivalent [Advanced Placement in the US], GCSE or equivalent [Grade 10 in the USA], other qualification, and none); and National Health Service-recommended shielding status for any household member (waves 1-5, COVID Surveys; denoted by yes/no). A history of physical morbidities was also captured (wave 10, Main Survey) and based on any mention of a cardiometabolic condition (congestive heart failure, coronary heart disease, angina, heart attack or infarction, stroke, diabetes, and/or hypertension); respiratory disease (respiratory disease comprised bronchitis, emphysema, chronic obstructive pulmonary disease, and/or asthma); or cancer of any type. Current psychological distress (wave 6, COVID Survey) was ascertained using the administration of the 12-item version of the General Health Questionnaire. Validated against standardised psychiatric interviews,17,18 this is a widely used measure of distress in population-based studies. Consistent with published analyses,19-21 we used a score of ≥3 to denote psychological distress.

*Assessment of vaccine intentionality*

At wave 6 in the COVID Survey, study members were asked “Imagine that a vaccine against COVID-19 was available for anyone who wanted it. How likely or unlikely would you be to take the vaccine?”. Possible responses were “Very likely”, “Likely”, “Unlikely” and “Very unlikely”. The latter two categories were combined to denote vaccine hesitancy.

*Statistical analyses*

It is well-replicated that performance on tests of cognitive abilities are positively inter-related, whereby people who score highly on one test of cognition tend to score well on another.22 This has led to the use of the term ‘general cognitive ability’, usually known as ‘g’. Accordingly, using scores from the six tests of cognitive function we generated a single general cognitive function variable. Computed using principal components analysis, the first unrotated component of the six cognitive tests was used as a single measure of cognitive function (variance explained: 42%; loadings: immediate recall 0.74, delayed recall 0.72, verbal fluency 0.59, serial sevens 0.49, number series 0.64, numerical problem solving 0.66). To summarise the relation between cognition and vaccine hesitancy, we used logistic regression to compute odds ratios with accompanying 95% confidence intervals. In these analyses we calculated effect estimates for tertiles of cognitive function scores and those for a unit (standard deviation) disadvantage in score. The most basic analyses were adjusted for age, sex, and ethnicity. Retaining these covariates, we then explored the impact of separately controlling for existing somatic medical conditions, mental health, education, and shielding status.

**Results**

In a sample of 11,955 individuals who responded in full to the enquiry regarding COVID-19 vaccine intentionality, 17.2% (N=1842) indicated that they were hesitant (figure 1). In table 1 we show unadjusted study member characteristics according to vaccine intention. Relative to the group who indicated a willingness to have the vaccine, those who were hesitant were more likely to be young, female, from an ethnic minority background, and be less well educated. The hesitant were also less likely to carry an array of existing somatic morbidities and be shielding or live with someone who was. The prevalence of psychological distress was somewhat higher in the vaccine hesitant.

There were also differences in mental health between the vaccine groups

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To gain some information about whether the association with vaccine hesitancy was linear, the analyses were repeated according to tertiles of cognitive function. In age-, sex- and ethnicity- adjusted analyses, relative to people in the highest-scoring cognition tertile, those in the lowest were twice as likely to be vaccine hesitant (1.99; 1.66, 2.40). People in the intermediate ability tertial had intermediate risk of hesitancy (1.28; 1.07, 1.54) such that an incremental effect was apparent across the cognition categories (p-value for trend: <0.0001). Lastly, in order to explore inflections in the cognition–hesitancy association, we utilised deciles of cognition in analyses. Again, there was evidence of a clear trend, although this was not perfectly stepwise across all categories (figure 2).

**Discussion**

**Our main finding was that, in data collected immediately XXXXXX These effects were apparent across the full range of cognition scores. That we were able to replicate known predictors of COVID-19 vaccine hesitancy – being female,23-25 younger,23,25 non-white ethnicity,7,25,26 and having a lower prevalence of physical morbidity27 – gives us some confidence in our novel results for cognitive function.**

***Comparison with existing studies***

**To the best of our knowledge, there has been one prior examination of the relationship between cognition and vaccine hestinacy.**2 **Comprising two small cross-sectional studies where data collection took place before the announcement of vaccine test results, people who performed better on a short test of cognitive function were more likely to be vaccine-accepting.**2 **We found similar results in using more detailed measures of cognitive function in a large sample which allowed us to explore the shape of the relationship across the full range of abilities. A closely related literature is that for education with which cognition is positively correlated.28 This supports the present results whereby people with higher educational achievement were less likely to be vaccine-hesitant. 29,30**

***Potential public health implications***

We have recently shown that, in data collected prior to vaccine distribution, of a range of baseline psychosocial factors which included socioeconomic status, education, personality type, and mental health, cognitive function was the most strongly associated with subsequent incidence of severe COVID-19, such that a doubling of the risk of hospitalisation was apparent in the lowest scoring group.31 This supports other data that individuals with higher cognitive function experience a lower risk of death from other respiratory diseases, including influenza and pneumonia.32 The notion that people with lower cognitive ability appear to have greater rates of severe COVID-1931,33 and, based on the present results are also less likely to take up the offer of vaccination, may further increase the disease burden in this group, as may also be the case for people from ethnic minority groups7,34 and the socioeconomically disadvantaged.2,31

***Plausible explanations***

Various explanations may be germane to the cognition–vaccine intention link, including the observation that people with higher cognitive ability are better equipped to obtain, process, and respond to disease prevention advice.35 There has been a deluge of health advice in the current pandemic during an era when news outlets and social media platforms have never been more ubiquitous and influential. Preventative information has ranged from the simple and practical to the complex, contradictory, false, and fraudulent. In order to diminish their risk of the infection, people have to acquire, synthesise, weigh-up, and deploy this information but the ability to do so seems to vary by levels of health literacy36 just as it may for its close correlate, cognitive function.

***Study strengths and weaknesses***

**While the present study has its strengths, including its size, national representativeness, and timing, there are also some weaknesses. First, we used vaccine intentionality as an indicator vaccine uptake but the correlation is imperfect. In a small scale longitudinal study conducted during the period of the 2009 H1N1 pandemic in Hong Kong, less than 10% of people who expressed a commitment to being inoculated reported that they had received a vaccination two months later.37 Elsewhere, in a US adult population at high risk of seasonal influenza, around half of those intending to be vaccinated had received the inoculation within the following 5 months.38 Second, there was inevitably some loss to follow-up (figure 1). While this attrition may have impacted upon the estimation of the prevalence vaccine hesitancy which is likely to be lower in our select sample relative to the general population,39 it is unlikely to have influenced our estimation of its relationship with cognitive function. Thus, in other contexts, we have shown that highly select cohorts reveal very similar risk factor–disease associations to those seen in studies with conventionally high response.40**

**In conclusion, people with lower scores on standard tests of cognitive function reported being less willing to take up the future offer of vaccination for COVID-19.** **It is possible that erroneous social media news reports have complicated decision-making. Special efforts should be made to communicate clear information about vaccine efficacy and safety so that everyone—including those who report being less likely to choose vaccination—can make well-informed choices.**

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**Figure 1. Flow of cohort members into the analytical sample:**

**Main Survey and COVID Survey in Understanding Society**

(Drew: we’ll want some version of this. But please prioritise tables 1 and 2 for now)

50,994 participants in Wave 1 of Main Survey (2009-11)

N=7361 with full data on cognition, intention, and covariates

N=11,955 with full data on vaccine intentionality

Wave 6 (N=12,035) of COVID Survey

(Nov 2020)

*(vaccine hesitancy, psychological distress)*

Wave 1 (N=17,761) COVID Survey

(April 2020)

34,318 participants in Wave 10 of Main Survey

(*educational level, ethnicity, history of comorbidity*)

40,730 participants in Wave 3 of Main Survey (2011-13)

(*cognitive function*)

42,330 participants in Waves 8 (2016-18) and 9 (2017-19) of Main Survey

**Figure 2. Odds ratios (95% CI) for the relation of psychological distress with**

**COVID-19 vaccine hesitancy in Understanding Society**

(Drew: all the better if we can use the original 13 point scale (lowest risk being zero) here – assuming sufficient numbers. But please prioritise tables 1 and 2 for now)

|  |
| --- |
|  |
|  |
| All covariates are: age, sex, ethnicity, somatic comorbidity, psychological distress, shielding, and education. In both models, the p-value for trend across deciles was <0.0001 |

**Table 1. Study member characteristics according to COVID-19 vaccine hesitancy in**

**Understanding Society** (Drew: we should have the same version of this, though the sample size might differ)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Vaccine hesitant** | | **P value** |
|  | **Yes** | **No** |  |
| Numbers of people (%) |  |  |  |
|  |  |  |  |
| **Demographic factors** |  |  |  |
| Age, yr, mean (SD) |  |  |  |
| Female, N (%) |  |  |  |
| Non-white ethnicity, N (%) |  |  |  |
|  |  |  |  |
| **Socioeconomic factors** |  |  |  |
| No university education, N (%) |  |  |  |
|  |  |  |  |
| **Physical comorbidities** |  |  |  |
| Cardiometabolic disease, N (%) |  |  |  |
| Respiratory disease, N (%) |  |  |  |
| Any cancer, N (%) |  |  |  |
|  |  |  |  |
| **Psychological morbidities**, N (%) |  |  |  |
| *Physician diagnosis* |  |  |  |
| Anxiety |  |  |  |
| Depression |  |  |  |
| Psychosis or schizophrenia |  |  |  |
| Bipolar disorder or manic depression |  |  |  |
| An eating disorder |  |  |  |
| Post-traumatic stress disorder |  |  |  |
| ‘Other’ |  |  |  |
| Any of the above |  |  |  |
| *General Health Questionnaire* |  |  |  |
| Psychological distress, mean (SD) |  |  |  |
| Psychological distress, N (%) |  |  |  |
| * asymptomatic (score 0) |  |  |  |
| * subclinically symptomatic (1-3) |  |  |  |
| * symptomatic (4-6) |  |  |  |
| * highly symptomatic (7-12) |  |  |  |
|  |  |  |  |
| **Cognitive function** |  |  |  |
| *g* factor, mean (SD) |  |  |  |
|  |  |  |  |
| **Other** |  |  |  |
| Shielding in the household, N (%) |  |  |  |
|  |  |  |  |

Numbers of study members corresponds to those with complete data

on vaccine intentionality only

**Table 2. Odds ratios (95% CI) for the relation of psychological distress with**

**COVID-19 vaccine hesitancy in Understanding Society**

(Drew: My aim here is to show the apparently contrasting results for physical and psychological morbidity, though the story might not be quite so neat. Depending on the results, we may want a figure depicting these effects too – not for your first pass of the analyses though)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Number hesitant / Total at risk** | **Age, sex, & ethnicity** | **Age, sex, ethnicity, & comorbidity\*** | **Age, sex, ethnicity, & shielding** | **Age, sex, ethnicity, & education** | **Age, sex, ethnicity, & cognition** | **All covariates** |
|  |  |  |  |  |  |  |  |
| **Physician diagnosis\*\*** |  |  |  |  |  |  |  |
| Anxiety |  |  |  |  |  |  |  |
| Depression |  |  |  |  |  |  |  |
| Psychosis or schizophrenia |  |  |  |  |  |  |  |
| Bipolar disorder or manic depression |  |  |  |  |  |  |  |
| An eating disorder |  |  |  |  |  |  |  |
| Post-traumatic stress disorder |  |  |  |  |  |  |  |
| ‘Other’ |  |  |  |  |  |  |  |
| Any of the above |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| **Psychological distress** |  |  |  |  |  |  |  |
| Asymptomatic (score 0) |  | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) |
| Subclinically symptomatic (1-3) |  |  |  |  |  |  |  |
| Symptomatic (4-6) |  |  |  |  |  |  |  |
| Highly symptomatic (7-12) |  |  |  |  |  |  |  |
| P for trend |  |  |  |  |  |  |  |
| Per SD (XX points) decrease |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
| **Physical comorbidities\*\*** |  |  |  |  |  |  |  |
| Cardiometabolic disease |  |  |  |  |  |  |  |
| Respiratory disease |  |  |  |  |  |  |  |
| Any cancer |  |  |  |  |  |  |  |
| Any of the above |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |

Numbers of study members in this sample corresponds to those with complete data on all variables in the analyses. \*for physical comorbidities, adjustment is for psychological morbidities, and vice versa; \*\*comparator group is those study members without the condition