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Article

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The COVID-19 pandemic has seen digital contact tracing emerge around the world to help prevent spread of the disease. A mobile phone app records proximity events between app users, and when a user tests positive for COVID-19, their recent contacts can be notified instantly. Theoretical evidence has supported this new public health intervention^{1–6}, but its epidemiological impact has remained uncertain⁷. Here we investigated the impact of the NHS COVID-19 app for England and Wales, from its launch on 24 September 2020 through to the end of December 2020. It was used regularly by approximately 16.5 million users (28% of the total population), and sent approximately 1.7 million exposure notifications: 4.4 per index case consenting to contact tracing. We estimated that the fraction of app-notified individuals subsequently showing symptoms and testing positive (the secondary attack rate, SAR) was 6.0%, comparable to the SAR for manually traced close contacts. We estimated the number of cases averted by the app using two complementary approaches. Modelling based on the notifications and SAR gave 284,000 (108,000–450,000), and statistical comparison of matched neighbouring local authorities gave 594,000 (317,000–914,000). Roughly one case was averted for each case consenting to notification of their contacts. We estimated that for every percentage point increase in app users, the number of cases can be reduced by 0.8% (modelling) or 2.3% (statistical analysis). These findings provide evidence for continued development and deployment of such apps in populations that are awaiting full protection from vaccines.

The United Kingdom has been hit heavily by the COVID-19 pandemic, recording one of the highest confirmed death rates in the world in 2020. To reduce spread of the virus, the NHS COVID-19 app for England and Wales was launched on 24 September 2020. Out of 33.7 million eligible people with compatible smartphones, the app has been downloaded on 21 million unique devices, and is regularly used by at least 16.5 million people. The main function of the app is digital contact tracing^{1–6} using the privacy-preserving Google Apple Exposure Notification (GAEN) system, embedded in the Android and iOS operating systems^{8,9}, supplemented with custom Bluetooth processing algorithms¹⁰. App users are notified and instructed to quarantine if they had contact with another user later confirmed to have COVID-19, if the exposure had characteristics that exceed a risk threshold. Digital tracing is a novel public health measure, with unknown epidemiological impact⁷. Other functions of the NHS app include providing locally appropriate information on COVID-19 prevention, checking into venues using a custom QR code scanner (allowing later notification if users have visited risky venues), and a symptom checker linked to the booking of tests. For tests booked through the app, the test result triggers a set of

actions automatically, including notification of the tested individual through the app, and digital contact tracing for positive results (upon the user's approval).

When installing the app, users enter their postcode district (the first half of the postcode), allowing analysis of geographic variation in app use. We aggregated data at the level of lower tier local authorities (LTLAs), of which there are 338 in England and Wales, to match case data. App uptake - the fraction of active users in the population - was variable between LTLAs (Figure 1a, c), with an interquartile range of 24.2–32.4%. We defined three phases for the analysis, annotated in Figure 1d: phase 0 before app launch, phase 1 from 1 October to early November 2020 (first version of app) and phase 2 from early November to 31 December 2020 (improved version of app). These are described in more detail in Extended Data Table 1. Phases in the app precede phases in the resulting cases: there is a lag between changes in transmission rates and changes in confirmed cases, we assumed by 8 days. Other factors beside the app changed during these phases, including locally targeted control measures, a national lockdown, and a surge in cases in December, mostly driven by the new variant B.1.1.7.

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Roughly 1.7 million notifications were sent as a result of 560,000 app users testing positive over the whole time period: a mean number of notifications per index case of 3.2. 72% of app-using index cases consented to digital tracing upon testing positive, therefore the mean number of notifications per tracing event was 4.4. Numbers of notifications over time are shown in Extended Data Figure 1B.

We estimated the secondary attack rate (SAR) in app-notified individuals: the probability that someone who is notified will report a positive test during the recommended quarantine or in the following two weeks. We estimated an SAR of 6.02%, with confidence interval 5.96 - 6.09% though sensitivity analyses suggest a precision of roughly 5-7%. These results indicate that the app is functioning at a technical level, as also recently demonstrated for the Swiss and Spanish apps^{11,12}.

To evaluate the epidemiological impact of the app, we first used a modelling approach. We estimated the number of cases averted with a model linking the number of notifications, the probability that those notified were cases, the timing of notification relative to transmission, and adherence to quarantine. The latter is critical but hard to assess reliably. UK surveys found only 11% of individuals in quarantine declared proper adherence to quarantine rules, but 65% of individuals intended to adhere to quarantine¹³, albeit imperfectly. Recent surveys found a high adherence to quarantine (greater than 80%)¹⁴, and this behaviour may be more representative of app users. We considered an intermediate scenario corresponding to 61% overall effectiveness of quarantine in preventing transmissions as our central estimate, leading to 284,000 cases averted. The estimated number of cases averted was higher in areas of high app uptake (Figure 2). The slope of the regression in Figure 2b indicates that the fraction of cases averted (among all cases observed or averted) increased by 0.8% for every 1% increase in app uptake (Table 1).

We used a second approach to evaluate the epidemiological impact of the app: linking variation in app uptake between LTLAs with variation in cumulative cases. We addressed strong confounding factors with a stratified approach, only comparing LTLAs with similar socio-economic properties and geography. We used several different ways of grouping LTLAs into comparable units, with similar results; one is described below, the others are described in Supplementary Information (their results are in Extended Data Tables 3 and 4, and Extended Data Figure 2).

Greater app use is associated with areas being more rural, with less poverty and greater local GDP (Supplementary Information Table 4), hence we adjusted for these measured confounding variables. Unmeasured confounders could include adherence to social distancing and face mask use; since these factors affected transmission before app release, app uptake should have some correlation with case numbers even before app release (phase 0). To test this, we regressed phase 0 case numbers on several covariates including later uptake of the app; app uptake was indeed associated (pure confounding). To adjust for this confounding, we stratified LTLAs into quintiles based on their phase 0 cases (Extended Data Figure 6), and only compared within these strata. This stratification removed the correlation between app uptake and pre-app cases, indicating that this has at least partially adjusted for unmeasured confounders (Extended Data Table 2; Supplementary Information on confounding and placebo regression). Case numbers in an LTLA are also confounded by those in neighbouring LTLAs, therefore we only compared neighbouring (adjacent) LTLAs. We found that the difference in case numbers per capita between neighbouring LTLAs, matched by phase 0 case number quintile, was strongly and robustly associated with differences in app use, regardless of adjustment for other demographic confounders (Figure 2, Table 1, Extended Data Table 2).

Disaggregating the effect by phase, we found that it was larger during the second phase (Table 1). This is consistent with the increased number of notifications sent per index case implemented at the start of phase 2 (Extended Data Figure 1B). Table 1 shows the estimated effect

size replicated in different statistical analyses (see Supplementary Information for details).

We estimated the numbers of cases averted during phases 1 and 2 combined: 284,000 (108,000 - 450,000) from the modelling approach, and 594,000 (317,000 - 914,000) from the statistical approach. The ranges show a sensitivity analysis exploring 2.5-97.5% of the variability in modelling estimates, and a 95% CI for the statistical one. These estimates are comparable to the number of app users who tested positive and consented for notifications to be sent: roughly 400,000. This suggests that on average, each confirmed case who consented to notification of their contacts through the app prevented one new case, i.e. the whole transmission chain following each such case was 1 individual smaller. We translated these estimates into deaths averted during phases 1 and 2 using the case fatality rate observed for this period: 1.47% (see Methods). This gave 4,200 (1,600 - 6,600) deaths averted from the modelling approach, and 8,700 (4,700 - 13,500) from the statistical approach. For comparison, the total number of cases and deaths that actually occurred in this period were 1,892,000 and 32,500, respectively. When cases were averted is shown in Extended Data Figure 3.

Finally, we extrapolated the findings to explore different ways in which the app could be improved, by re-running scenarios with different parameters (Table 2). These are retrospective projections; however, the expected reductions in cases are relevant when considering forward projections.

Discussion

Our analysis suggests a large number of COVID-19 cases were averted by contact tracing via the NHS app, ranging from approximately 100,000 to 900,000 depending on methodological details. For comparison, 1.9 million cases actually arose. Averted cases were concentrated in Phase 2, covering November and December 2020, after a major upgrade to the app's risk scoring function¹⁰. This finding is similar to prior results from modelling: using our individual-based model¹⁵, a 30% app uptake was estimated to avert approximately 1 infection for every 4 infections arising during 4.5 months of action⁴.

Though it is informative to estimate effects on the time-varying reproduction number e.g.¹⁶, we did not pursue such an analysis here. The epidemic dynamics of individual LTLAs are difficult to interpret: the period of analysis coincided with staggered introductions of locally targeted restrictions, a short national lockdown, the Christmas holiday season, and the emergence of the B.117 variant genotype, which is more infectious and rapidly spread across the country¹⁷⁻²⁰. Future work could perhaps model all of these effects in a single hierarchical model, permitting joint estimation of the app effect over LTLAs with linked drivers and dynamics. Our simpler approaches have the benefit of transparency, and we hypothesise that under negative-feedback dynamics (greater local spread triggering greater local control measures), appropriately constructed comparisons of total case counts over an appropriate period may reveal underlying propensity for disease spread.

The main limitation of our analysis is that it is an observational study: no randomized or systematic experiment resulted in different app uptake in different places. Interpreting observational analyses requires particular care due to the risk of confounding. We therefore used two approaches: mechanistically modelling the app's function, and a statistical approach. Our statistical approach was stratified to focus on differences between directly comparable areas only, emulating how a cluster randomised trial would have been conducted²¹. Our placebo analysis suggested that our adjustment for confounders largely removed their effect; however, it is still possible that changes in app use over time and across geographies reflect changes in other interventions, and that our analysis incorrectly attributes the effect to the app. Such residual confounding, if present, would mean that our statistical estimate for cases averted is too high and our modelling estimate is more accurate.

Conversely, there could be a genuine albeit indirect effect of the app, whereby users maintain a greater distance from others than they otherwise would have done, aware that the app monitors distance and could later advise quarantine. This would mean that our modelling estimate (derived only from the app's direct effect, proportional to the SAR) is too low, and our statistical estimate is more accurate. On balance, an effect size between the two estimates seems most likely. We discuss the expected effects of further biases in Supplementary Information.

The app is best understood as part of a system of non-pharmaceutical interventions, not in isolation⁷. It is not a substitute for social distancing or face masks: control of the epidemic requires all available interventions to work together. Isolation and quarantine can only be effective when financially supported. All contact tracing requires case finding, and so is a follow up to effective, widespread and rapid testing. The specific role of digital tracing is to speed up tracing, and to reach more people per index case. An advantage of the NHS app even compared to other digital tracing apps is its full integration with testing: tests ordered through the app trigger actions automatically, without requiring the user to enter their result in the app. Further improvement could perhaps be obtained with increased use of location-specific QR code scanning: notifications for 226 risky venue events have been issued as of 20 Jan 2021. Contact tracing backwards²² could help to identify risky venue events.

Digital tracing is not a substitute for manual tracing: both are valuable. We compare them in Supplementary Information Table 1, and summarise here. The SAR we estimated for the app, 6%, is similar to the SAR for manual contact tracing during December 2020 and January 2021 for 'close' contacts: 6.9%²³. We found the mean number of contacts traced per consenting index case was 4.4 for digital tracing, compared to 1.8 for manual tracing. A greater fraction of these contacts is expected to be outside of the household of the index case for the app, with smaller probability of already having been notified informally by the index, and so greater benefit of having been traced. This, and the speed of app notification (Extended Data Figure 4), suggests that the effect of tracing digitally was mostly additional to that of tracing manually. We confirmed this with an analysis that included adjustment for quality of manual tracing, which did not affect our conclusions.

The surest ways to increase the effectiveness of the programme are to increase uptake, and to provide material support to individuals undergoing isolation and quarantine. Special efforts may be needed to reach underserved communities. That testing should be as fast as possible to help prevent transmission is well known. This could perhaps be facilitated by point-of-care antigen tests and integration of self-testing with the app, though this would need investigation to establish accuracy and usability. Widespread vaccination will eventually reduce the need for non-pharmaceutical interventions, but vaccination will unlikely have global reach within the coming months, during which time improved non-pharmaceutical interventions could still prevent many infections^{24,25}. Smartphone use is already global, and thus privacy-preserving contact tracing apps should be further integrated into the public health toolkit.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information,

acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41586-021-03606-z>.

1. Ferretti, L. et al. Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. *Science* **368**, (2020).
2. Kretzschmar, M. E. et al. Impact of delays on effectiveness of contact tracing strategies for COVID-19: a modelling study. *Lancet Public Health* **5**, e452–e459 (2020).
3. Lunz, D., Batt, G. & Rues, J. To quarantine, or not to quarantine: A theoretical framework for disease control via contact tracing. *Epidemics* **34**, 100428 (2020).
4. Abueg, M. et al. Modeling the combined effect of digital exposure notification and non-pharmaceutical interventions on the COVID-19 epidemic in Washington state. *bioRxiv* (2020) <https://doi.org/10.1101/2020.08.29.20184135>.
5. Lambert, A. A mathematically rigorous assessment of the efficiency of quarantining and contact tracing in curbing the COVID-19 epidemic. *bioRxiv* (2020) <https://doi.org/10.1101/2020.05.04.20091009>.
6. Cencetti, G. et al. Digital proximity tracing in the COVID-19 pandemic on empirical contact networks. *bioRxiv* (2020) <https://doi.org/10.1101/2020.05.29.2015915>.
7. Colizza, V. et al. Time to evaluate COVID-19 contact-tracing apps. *Nat. Med.* **27**, 361–362 (2021).
8. Google/Apple. *Exposure Notifications: Helping fight COVID-19 - Google*. https://www.google.com/intl/en_us/covid19/exposurenotifications/ (2020).
9. Troncoso, C. et al. Decentralized Privacy-Preserving Proximity Tracing. *arXiv* [cs.CR] (2020).
10. Lovett, T. et al. Inferring proximity from Bluetooth Low Energy RSSI with Unscented Kalman Smoothers. *arXiv* [eess.SP] (2020).
11. Salathé, M. et al. Early evidence of effectiveness of digital contact tracing for SARS-CoV-2 in Switzerland. *Swiss Med. Wkly* **150**, w20457 (2020).
12. Rodriguez, P. et al. A population-based controlled experiment assessing the epidemiological impact of digital contact tracing. *Nat. Commun.* **12**, 587 (2021).
13. Smith, L. E. et al. Adherence to the test, trace and isolate system: results from a time series of 21 nationally representative surveys in the UK (the COVID-19 Rapid Survey of Adherence to Interventions and Responses [CORSAIR] study). (2020) <https://doi.org/10.1101/2020.09.15.20191957>.
14. Fancourt, D., Bu, F., Wan Mak, H. & Steptoe, A. *Covid-19 Social Study*. (2020).
15. Hinch R and Robert WJM et al. OpenABM-Covid19 - an agent-based model for non-pharmaceutical interventions against COVID-19 including contact tracing. (2020) <https://doi.org/10.1101/2020.09.16.20195925>.
16. Flaxman, S. et al. Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. *Nature* **584**, 257–261 (2020).
17. Volz, E. et al. Transmission of SARS-CoV-2 Lineage B.1.1.7 in England: Insights from linking epidemiological and genetic data. *bioRxiv* (2021) <https://doi.org/10.1101/2020.12.30.20249034>.
18. Davies, N. G. et al. Estimated transmissibility and severity of novel SARS-CoV-2 Variant of Concern 202012/01 in England. *bioRxiv* (2020) <https://doi.org/10.1101/2020.12.24.20248822>.
19. Vöhringer, H. et al. Lineage-specific growth of SARS-CoV-2 B.1.1.7 during the English national lockdown. <https://virological.org/t/lineage-specific-growth-of-sars-cov-2-b-1-7-during-the-english-national-lockdown/575> (2020).
20. Public Health England. *Investigation of novel SARS-CoV-2 variant - Variant of Concern 202012/01 - TC2*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949639/Technical_Briefing_VOC202012_2_Briefing_2_FINAL.pdf (2020).
21. Hernán, M. A. & Robins, J. M. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am. J. Epidemiol.* **183**, 758–764 (2016).
22. Endo, A. et al. Implication of backward contact tracing in the presence of overdispersed transmission in COVID-19 outbreaks. *Wellcome Open Res* **5**, 239 (2020).
23. Public Health England. *Investigation of novel SARS-CoV-2 variant - Variant of Concern 202012/01 - TC3*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950823/Variant_of_Concern_VOC_202012_01_Technical_Briefing_3_England.pdf (2020).
24. Galanti, M. et al. The importance of continued non-pharmaceutical interventions during the upcoming SARS-CoV-2 vaccination campaign. *bioRxiv* (2020) <https://doi.org/10.1101/2020.12.23.20248784>.
25. Moore, S., Hill, E. M., Tildesley, M. J., Dyson, L. & Keeling, M. J. Vaccination and Non-Pharmaceutical Interventions: When can the UK relax about COVID-19? *bioRxiv* (2021) <https://doi.org/10.1101/2020.12.27.20248896>.

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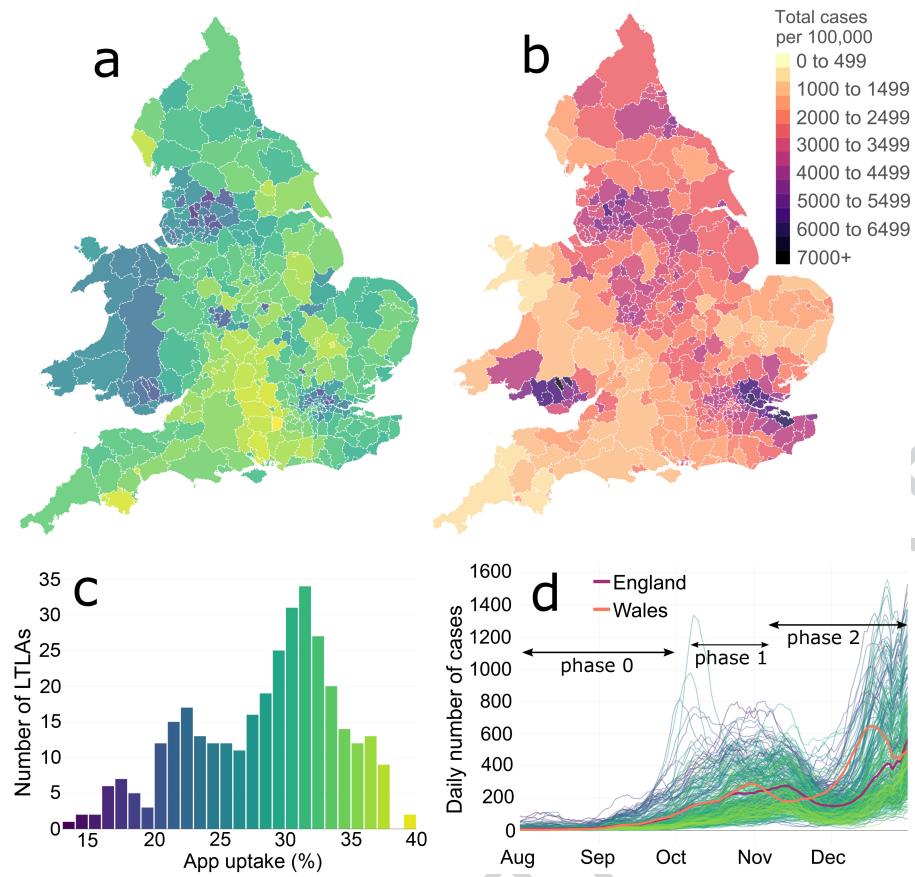


Fig. 1 | Geographical variability of app uptake and COVID-19 cases. A: a map of app uptake by Lower Tier Local Authority (LTLA) with colours as in panel C. B: COVID-19 cases per 100,000 population, cumulative over our analysis phases 1 and 2. C: as panel A, but as a histogram. D: the seven-day rolling mean of daily

COVID-19 cases per 100,000 population, one line per LTLA, coloured by app uptake as in panel C. Values for England and Wales are also shown. Black horizontal arrows indicate our analysis phases. Panels B and D show case numbers in the whole LTLA population, not just in app users.

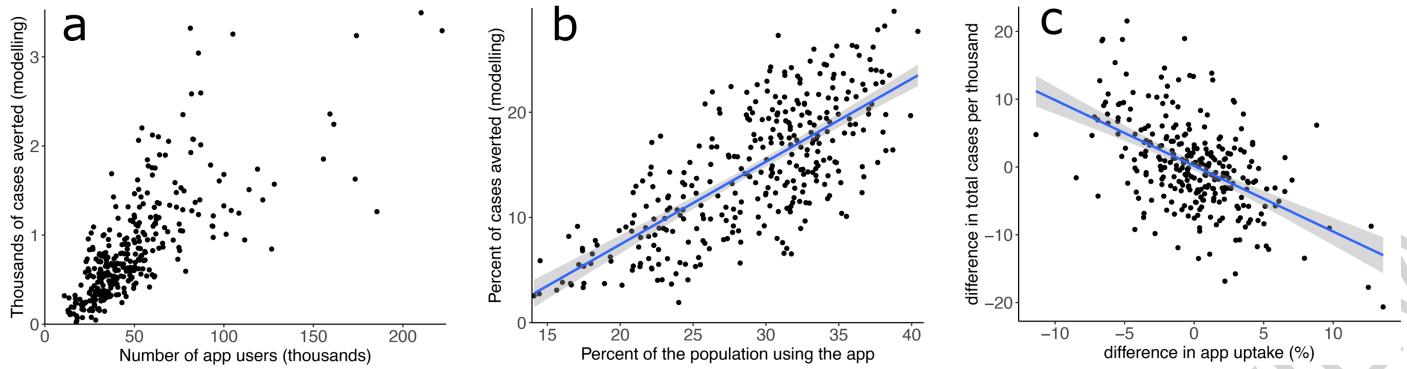


Fig. 2 | The link between app use and cases averted in each LTLA.

A: estimated number of cases averted in Phases 1 and 2 combined, versus number of app users. B: as panel A, but with percentages instead of numbers.

C: the unadjusted relationship between difference in app uptake and difference

in number of cases per capita in Phases 1-2 combined. In panels B and C, the blue line shows the least-squares fit of the y axis variable to the x axis variable, and the shaded grey area shows the associated 95% confidence interval.

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Table 1 | The estimated effect of the app

Secondary Attack Rate among individuals notified by the app		6%
Cases/deaths averted in phases 1&2:	Cases	Deaths
from modelling of digital tracing	284,000 (108,000 - 450,000)	4,200 (1,600 - 6,600)
from matched neighbours regression	594,000 (317,000 - 914,000)	8,700 (4,700 - 13,500)
Percent reduction in cases for every percent increase in app use		
Main analysis	Phase 1	Phase 2
Modelling	0.33 (0.13 - 0.49)	0.93 (0.46 - 1.24)
Matched neighbours regression	1.09 (0.04 - 2.14) (bootstrap: 0.15 - 2.16)	2.66 (1.75 - 3.56) (bootstrap: 0.80 - 4.71)
Secondary analyses	Phase 1	Phase 2
Stratified linear regression in clusters*	-1.05 (-2.08 - -0.04)	3.34 (2.53 - 4.14)
Matched pairs regression*	5.08 (1.77 - 8.40)	3.89 (1.05 - 6.74)
Matched pairs regression adjusted for local efficiency of manual contact tracing*	4.49 (0.21 - 8.77)	3.11 (-0.14 - 6.35)
Overall		

The effect is measured as the percent reduction in cases for every percent increase in app use, from different analyses. Ranges shown are 95% confidence intervals (CIs) for regressions, and a sensitivity analysis exploring 2.5%-97.5% of the distribution of outcomes for modelling. Analyses marked *** are restricted to England only, using data on the national NHS Test & Trace program aggregated by Upper Tier Local Authority. The measure of manual contact tracing quality is the proportion of contacts reached per case.

Table 2 | Scenarios for improvements

Analysis	Percent reduction in total case burden in phase 2 (in addition to reductions observed for the current implementation of the app)	
	Modelling	Statistical extrapolation
Increase uptake to 35.9% - current 90th percentile - for all LTLAs (Improve equity)	11% (5-15%)	21.0% (14.5-26.8%)
Increase uptake across the board by 20 percentage points (Mass improvement)	24% (10-34%)	41.5% (29.5-51.5%)
Switch to opt-out notification (5% drop-off)*	6.6% (2.5-11%)	Not applicable with this method
Improve adherence to quarantine by 20 percentage points	6.8% (5-8.7%)	Not applicable with this method
Reduce time to test result by one day**	3.6% (0.6-6.7%)	Not applicable with this method

Results are the percent reduction in total case burden that would have occurred during phase 2. This is the further reduction relative to the cases that actually occurred, not relative to cases inferred in the absence of the app. Ranges shown are 95% CIs for regressions, 2.5-97.5% sensitivity intervals for modelling. *Currently, the app requires consent after the receipt of a positive test for contact tracing to be initiated, which is provided by 72% of users. We assume that changing to opt-out consent, e.g. by consent at registration, would increase this to 95%. **Reducing test turnaround time has many benefits not modelled here; we consider only faster digital tracing

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Methods

Estimating app uptake

To monitor the safe function of the app and enable its evaluation, a limited amount of data are shared with a secure NHS server. Each active app sends a single data packet daily. The fields in these packets contain no sensitive or identifying information, and are approved and publicly listed by the Information Commissioner [<https://www.gov.uk/government/publications/nhs-covid-19-app-privacy-information>]. The raw data fields we used are described in Supplementary Information Table 2; further variables derived from these are described in Supplementary Information Table 3. A schematic illustration of data gathering is shown in Extended Data Figure 5. For the reported numbers of downloads, repeat downloads to the same phone are counted only once. The number of *active* users each day is defined as the number of data packets received by the NHS server; for a single representative value of this quantity, we took the mean over all days from November 1st to December 11th (earlier data was deemed less reliable). We note that there continue to be unexplained fluctuations in reported user numbers on Android phones. To estimate uptake within an LTLA, each postcode district was mapped to the LTLA in which the majority of its population reside, and we took the ratio (number of active users in postcode districts mapped to this LTLA) / (total population in postcode districts mapped to this LTLA). The population of England and Wales is 59.91 million, of whom 47.48 are over 16 and thus eligible to use the app [ONS]. Assuming that England and Wales is representative of the UK, we estimate that 82% of people aged 16+ have smartphones [OFCOM], and that of smartphones in circulation, 87% support the Google Apple Exposure Notification system [Department of Health and Social Care, personal communication]. The denominators for measuring uptake at the national level are therefore 59.91 million (total population) and 33.87 million (eligible population with compatible phones).

Defining numbers of cases

The COVID-19 case numbers per day we used here are those reported at <https://coronavirus.data.gov.uk/>, by specimen date and LTLA. We obtained per-capita case numbers at the LTLA level by dividing by LTLA populations reported by ONS. Testing has been available through the NHS Test and Trace system in all areas throughout the period, with a median delay of less than 2 days from booking a test to receiving the result. Testing capacity has mostly exceeded demand, except for two weeks in early September. We assumed that case ascertainment has been relatively constant over the period of analysis, an assumption qualitatively supported by the unbiased ONS and REACT studies^{26,27}.

Estimating the SAR

We focussed on a period in December and January when the number of positive test results in app users could be disaggregated by whether the user had been recently notified or not. Even with this data, successive data packets sent by the same device are not linked to each other. This means that when a given number of notifications are sent on a particular day, the exact number of those individuals notified who later receive a positive test result is unknown, because of the lack of linkage over time. We therefore used a probabilistic model for how many positive test results we would expect among those recently notified, as a function of the number of notifications on previous days, of the estimated delay from notification to testing positive, and of the SAR. We estimated the SAR by maximising the likelihood of this model. In detail: let $f_{NP}(t)$ be the probability that an individual notified on a given day then tests positive t days later (conditional on their testing positive at some later time, i.e. the function is normalised to 1). Let $N(t)$ be the number of individuals notified on day t , and $I_N(t)$ the number of individuals reporting a positive test on day t having been notified recently (either they are currently in the quarantine period recommended by the app, or the following 14 days). The number *expected* for the latter

is $SAR \times \sum_{t' \leq t} f_{NP}(t' - t)N(t')$ and we maximised a Poisson likelihood for the number observed, $I_N(t)$ (shown in Extended Data Figure 1D), given the number expected, treating observations from different days as independent. The confidence interval was obtained by likelihood profiling; however, sensitivity analyses suggested greater uncertainty (see Supplementary Information). $f_{NP}(t)$ was calculated as a convolution of the distributions for times from exposure to symptoms, from symptoms to testing positive, and from exposure to notification (see Supplementary Information). Our SAR calculation used only data from iPhones, excluding Android phones, for more stable daily numbers of analysis packets.

Modelling cases averted based on notifications and secondary attack rate

The effect of notifications received at time t on cases averted can be modelled as the product of (i) the number of notifications, (ii) the secondary attack rate, i.e. the probability that notified individuals are actually infected, (iii) the expected fraction of transmissions preventable by strict quarantine of an infectious individual after a notification, (iv) the actual adherence to quarantine, and (v) the expected size of the full transmission chain that would be originated by the contact if not notified. Before each notification, the contact's app sends a request for permission to the central NHS server. We estimated the total number of notifications per day on each Operating System (OS: Android or iOS) from these requests. We estimated the number of notifications per LTLA from the number of partial days of quarantine (typically corresponding to the first day of quarantine, i.e. the day of notification) per day, OS and LTLA, rescaling it by a time- and OS-dependent factor to match the number of notifications per day and OS. The geographical variability in notifications after summing over time is shown in Supplementary Information Figure 1. The delay between last exposure and notification is assumed to follow a normal distribution, with time-dependent parameters estimated via Least Squares from the daily number of notifications and individuals in quarantine. The fraction of preventable transmissions is estimated from the delay distribution using the generation time distribution in²⁸ with mean 5.5 days. We assume 100% effectiveness of quarantine in preventing transmission with complete adherence, and 50% as central value for quarantine with imperfect compliance. Finally, the size of the epidemic chain triggered by a single case is computed assuming that local epidemics do not mix and that the extra cases do not affect the epidemic dynamic. See Supplementary Information for further details.

Statistical analysis

The main statistical analysis compared statistics for each LTLA, labelled x , to those of the set comprising all of its 'matched' neighbours $N(x) = \{n_1, n_2, n_3, \text{etc}\}$. The matched neighbours $N(x)$ were defined as other LTLAs that share a border with x and were in the same quintile for number of cases per capita in phase 0. Distributions showing the variability between LTLAs in the number of neighbours and number of matched neighbours are shown in Supplementary Information Figure 2. Stratification into quintiles (as opposed to deciles etc.) was chosen to balance power and sufficient adjustment; no other possibility was tried, to guard against investigator bias.

Each statistic of interest was averaged over the matched neighbours, weighting by population size, to obtain the mean value in the matched neighbours of x . This was compared to the statistic for x . Linear regression was carried out using, for each statistic of interest, the difference between its value in x and in its matched neighbours $N(x)$. The statistics we considered were: per capita number of cases in each phase; the fraction of the population using the app; a measure of rural/urban mix on a scale from 1 to 5, from the Office of National Statistics (ONS); a measure of local GDP per capita from the ONS, adjusted for rural/urban score; and a measure of the fraction of the population living in poverty before housing costs, from the ONS.

Our main regression was

$$\log(\text{cumulative cases per capita in } x) - \log(\text{cumulative cases per capita in } N(x)) =$$

$$\text{beta_rural_urban}^* (\text{rural/urban score of } x \cdot \text{rural/urban score of } N(x)) +$$

$$\text{beta_gdp_band}^* (\text{local GDP band of } x \cdot \text{local GDP band of } N(x)) +$$

$$\text{beta_poverty}^* (\text{percent of the population living in poverty in } x \cdot \text{percent of the population living in poverty in } N(x)) +$$

$$\text{beta_users}^* (\text{percent of the population using the app in } x \cdot \text{percent of the population using the app in } N(x)) +$$

$$\text{epsilon_residual}$$

where the different data points for the regression (the different values of x) were the set of LTLAs with at least one matched neighbour, excluding LTLAs with no matched neighbours. Cumulative cases were considered in each of the three phases separately or with phases 1 and 2, as reported in our results. The values of the beta coefficients we estimated are shown in Extended Data Table 2. We used a logarithmic transform for the response variable in our regression, because cases are generated by an exponential process (transmission) and so the rate at which the number of cases varies with the dose of a treatment (i.e. the extent of an intervention) is highly confounded with the absolute number of cases. A regression with quadratic effect of uptake and intercept at 0 produced very similar findings to the above regression with linear effect of uptake (not shown). We considered additional uncertainty in the regression due to redundancy in the differences approach, e.g. in comparing both LTLA x with LTLA n and LTLA n with LTLA x , described in the bootstrapping section of Supplementary Information.

Predictions for cases averted were found using the regression coefficient beta_uptake to linearly extrapolate log(cumulative cases per capita) for each LTLA to that expected for an uptake of 15% (or keeping cases counts as they were, if uptake was already less than 15%). Here we assumed that there is negligible benefit of app uptake below 15% (though this is not expected to be the case in settings where usage is clustered into high-uptake communities²⁹). The definition of beta_users in the regression equation above means it is the expected increase in log(cumulative cases per capita) associated with a one-percentage-point increase in app uptake, when keeping constant GDP, rural/urban mix, and level of poverty. Our central estimate of beta_users in this analysis was -0.023 for phase 1 and 2 combined; this means an increase in uptake of p percentage points is expected to be associated with a factor $\exp(-0.023 \times p)$ increase in the cumulative number of cases per capita in phases 1 and 2. An increase of $p=1$ percentage points in uptake means a decrease of 2.3% in cases as we reported above. We estimated the number of deaths averted by multiplying the number of cases averted by the crude case fatality rate.

Alternative regressions are described in Supplementary Information; their results are in Extended Data Tables 3 and 4, and Extended Data Figure 2.

Case fatality rate

The case fatality rate was estimated as the ratio of total deaths (27,922) to cases (1,891,777) for Phases 1 and 2 combined. To test for

heterogeneity, it was also estimated as the regression of local deaths to cases, but no substantial heterogeneity was observed (not shown). It is a lower-bound due to right censoring of the time series of deaths.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Data availability

Data access is managed by the DHSC. An application is underway to make all data necessary to reproduce our analyses available to accredited researchers through the Office for National Statistics <https://www.ons.gov.uk/aboutus/whatwedo/statistics/requestingstatistics/approvedresearcherscheme>. Data aggregated spatially and temporally is available at <https://stats.app.covid19.nhs.uk/>.

Code availability

The analysis was performed with custom R (version 4.0.2) code, available on GitHub at https://github.com/BDI-pathogens/nhs_covid_app_evaluation.

26. Steel, K. & Donnarumma, H. *Coronavirus (COVID-19) Infection Survey, UK: 8 January 2021*. <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronaviruscovid19infectionssurveypilot/8january2021> (2020).
27. Riley, S. et al. REACT-1 round 7 updated report: regional heterogeneity in changes in prevalence of SARS-CoV-2 infection during the second national COVID-19 lockdown in England. *bioRxiv* (2020) <https://doi.org/10.1101/2020.12.15.20248244>.
28. Ferretti, L. et al. The timing of COVID-19 transmission. *MedRxiv*, Publisher: Cold Spring Harbor Laboratory Press (2020).
29. Farronato, C. et al. How to Get People to Actually Use Contact-Tracing Apps. *Harvard Business Review* (2020).

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Author contributions Contributions have been categorised according to the CRedit taxonomy (<https://casrai.org/credit/>). Conceptualization: CW, LF, MB, CF. Data curation: CW, DT, MC, LM, MA. Formal Analysis: CW, LF, CF. Funding acquisition: CH, MB, CF. Investigation: CW, LF, DT, MC, LM, CF. Methodology: CW, LF, RH, LM, CF. Project administration: LAD, CH, MB, CF. Resources: MA, CH, MB, CF. Supervision: CH, MB, CF. Visualization: CW, DT, MK. Writing – original draft: CW, LF, CF. Writing – review & editing: all authors.

Competing interests DT, MC and MA are part of the app data analytics team. DT is employed by Zühlke and MA by Accenture; Zühlke and Accenture are contracted by the DHSC for app development and analytics. MB is Lead Scientist for the app. CW, LF, RH, LA-D, DB, MK, CH and CF have acted as advisors for the DHSC on the app. This work was funded by a Li Ka Shing Foundation award to CF, and by research grant funding from the UK Department of Health and Social Care (DHSC) to MB, CH and CF. The funders played no role in the design and conduct of the analysis. DHSC runs the app, and manages the secure data environment where the analyses conducted here were performed. DHSC led dissemination of the findings in the UK.

Additional information

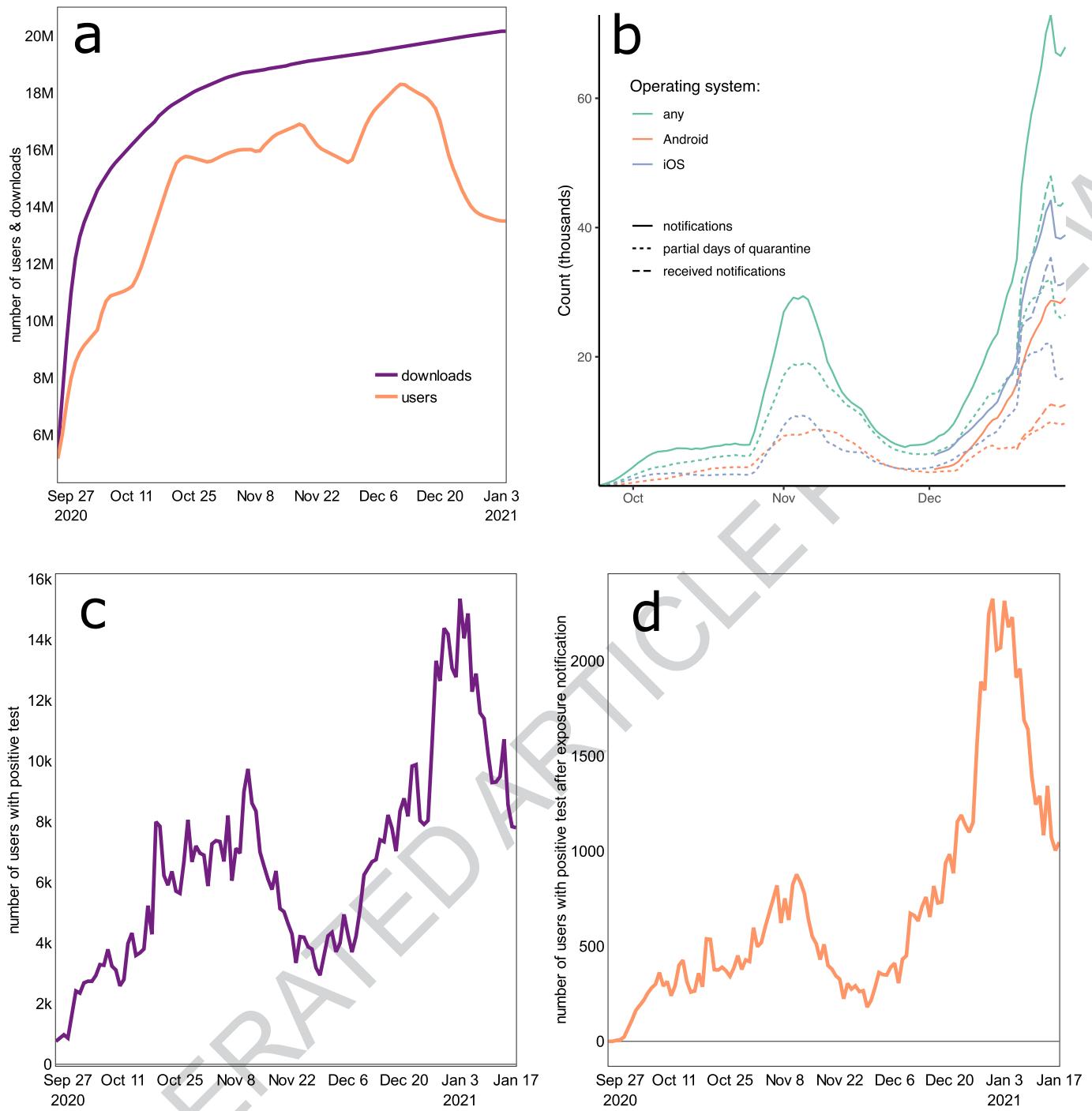
Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41586-021-03606-z>.

Correspondence and requests for materials should be addressed to C.F.

Peer review information *Nature* thanks Chiara Poletto, Jason Wang and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

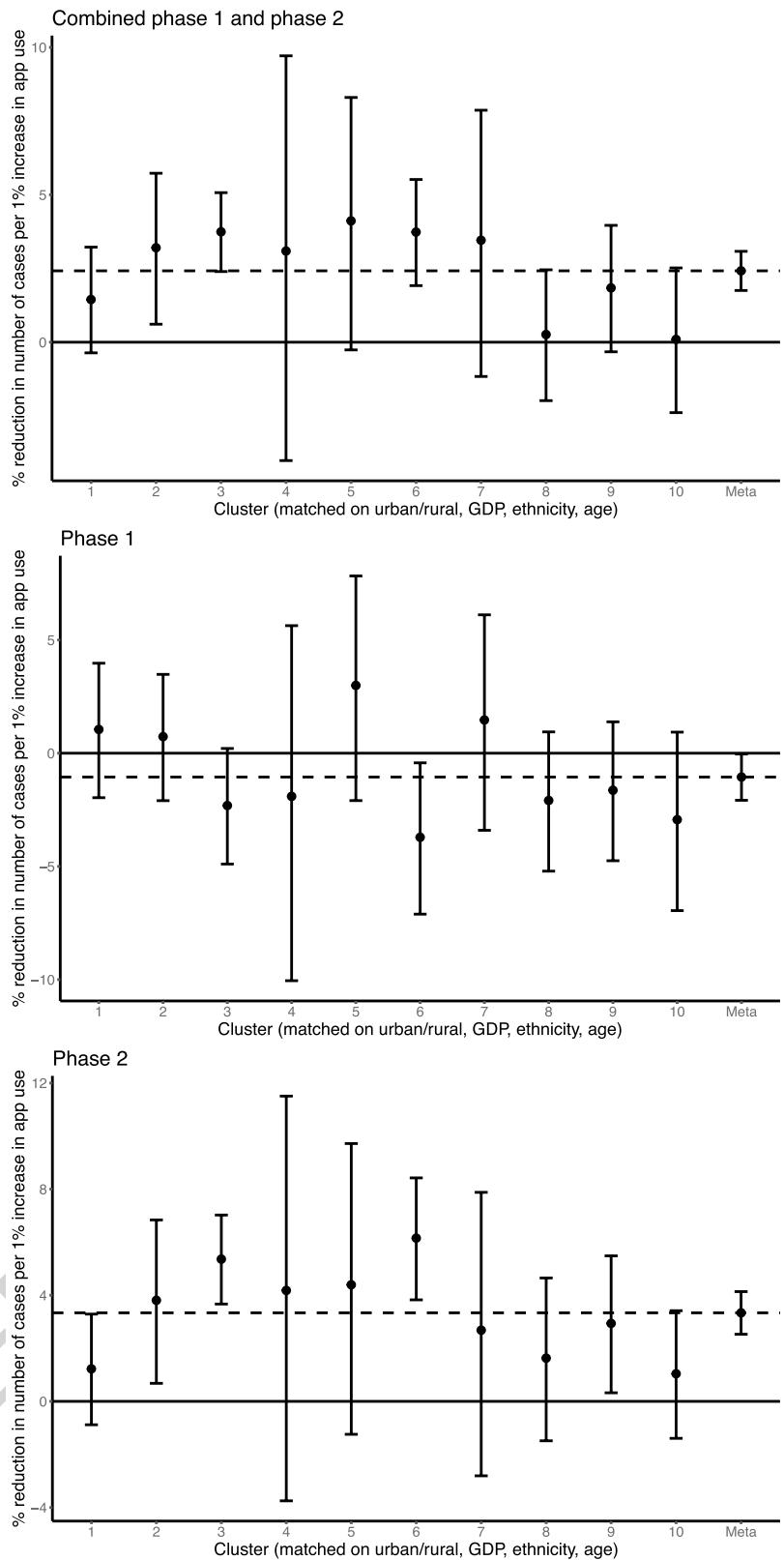
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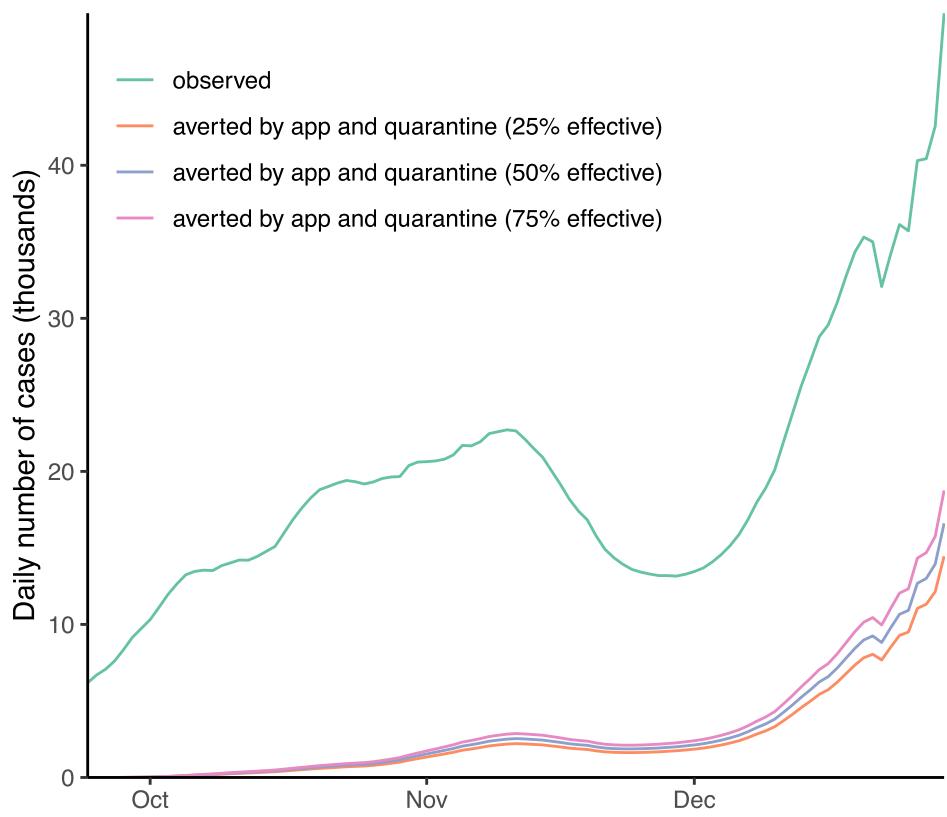
Extended Data Fig. 1 | Characterising the behaviour of the app. A: the total number of app downloads and active users over time. Fluctuations in app users are artifactual, driven by reporting issues on Android handsets, such that the estimate of 'active users' is a lower bound estimate. B: The seven-day rolling

mean of the total number of notifications triggered each day. C: the daily number of app users receiving a confirmed positive test. D: the daily number of app users recording a positive test result in the app, having recently received an exposure notification.



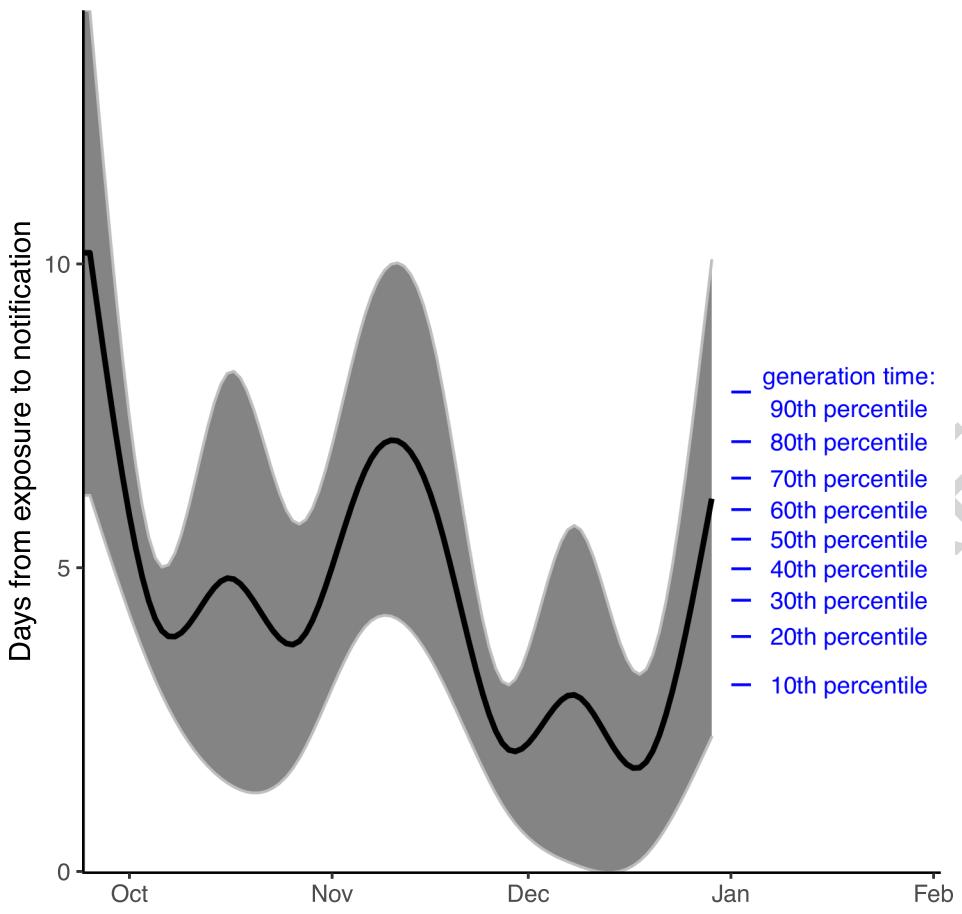
Extended Data Fig. 2 | Results for the secondary statistical analysis based on clusters. Regression coefficients for app effect for each cluster, and aggregate variance-weighted estimate (labelled ‘meta’). Error bars show 95%

confidence intervals. Panels are labelled for Phase 1 and 2 combined, and Phase 1 and Phase 2 separately. Aggregate estimates are reported in main text Table 1.



Extended Data Fig. 3 | Estimated cases averted over time. Plotted is the rolling 7-day average of the number of cases observed and predicted number of cases averted due to the notifications sent by the app, for different values of

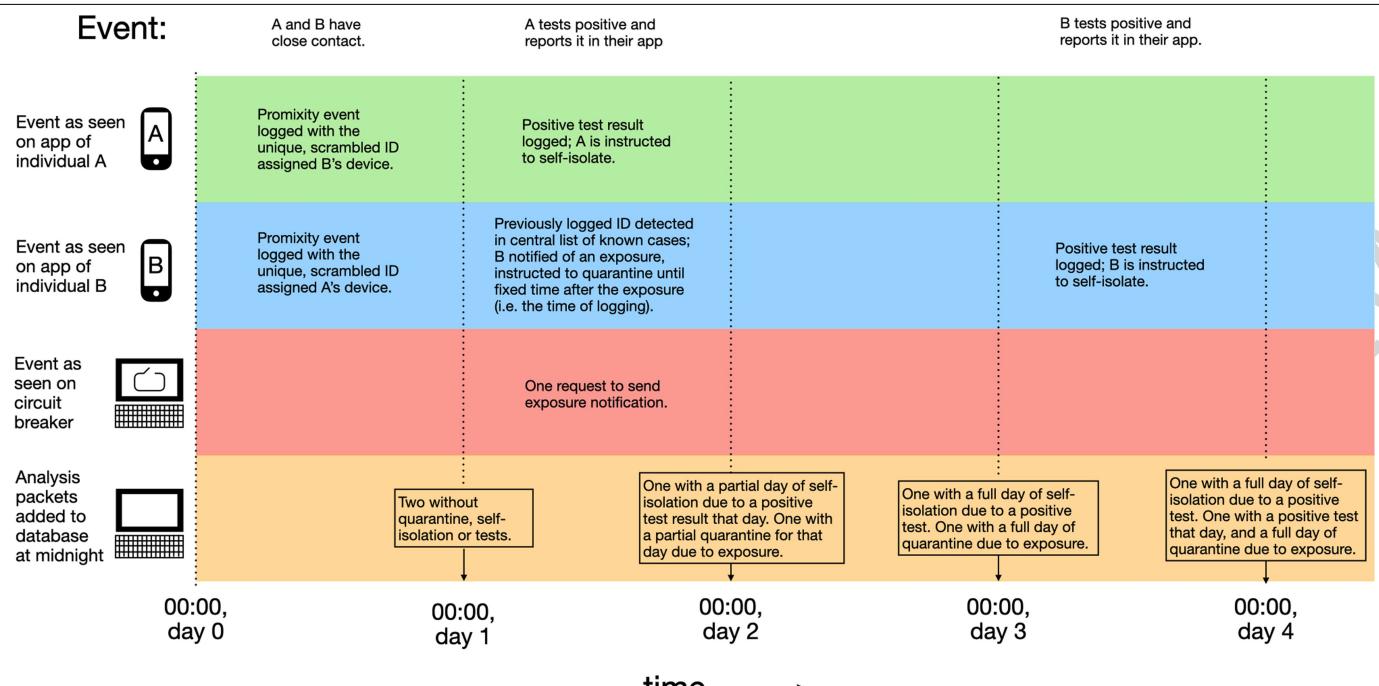
adherence to imperfect quarantine (25%, 50%, 75%) for the 31% of notified individuals who we assumed adhere imperfectly, in addition to 45.5% of notified individuals assumed to adhere perfectly.



Extended Data Fig. 4 | Estimated delay from exposure to notification. The black line shows the mean, and the grey ribbon around the mean shows points within 1 standard deviation of the mean. For comparison, deciles of the generation time distribution (the probability density function for the time

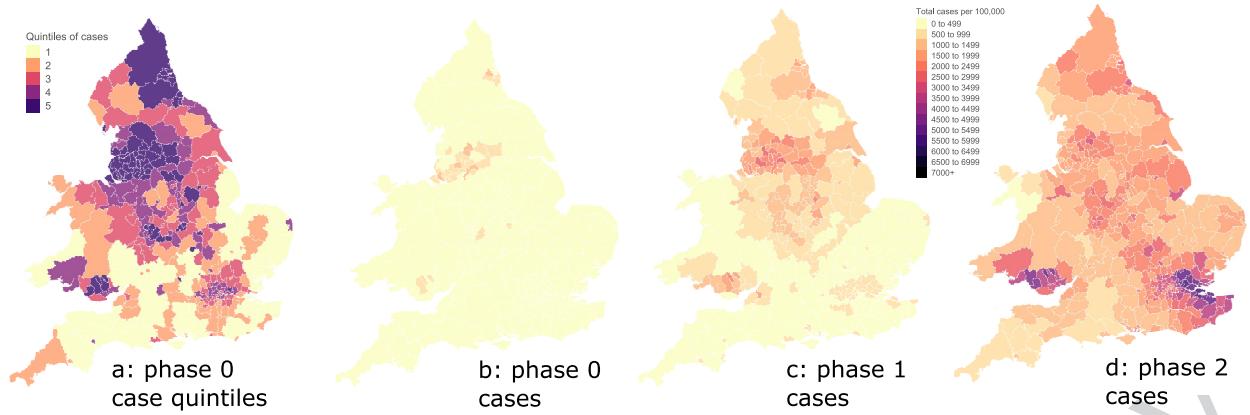
from becoming infected to infecting others) are shown in blue; for example the first decile (tenth percentile) is greater than the mean time to notification in December, i.e. the mean time to notification comes before 90% of when transmission would normally happen.

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Extended Data Fig. 5 | Summarising app data. We show the relationship between epidemiological events, and the data gathered about these by the app on individual phones and in the central database. The so-called circuit breaker

monitors and processes in real time requests by the app to notify (our quantity $N(t)$ in section “Estimate of the number of notifications” below.).



Extended Data Fig. 6 | Maps of per-capita numbers of cases in LTLAs over time. Panel a: per-capita case numbers in phase 0 grouped into quintiles, showing the stratification used for the main statistical analysis. Panels b, c and

d: actual per capita case numbers are shown, using a shared colour scale (shown once), for phases 0, 1 and 2 respectively.

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Extended Data Table 1 | Phases of our analysis

Phase	Date range for analysing cases*	Rationale	Additional context
0	1 Aug 2020 - 30 Sept 2020	Two months of baseline data before the introduction of the app. Used for adjustment and stratification of analyses. We ignore the effects of pilot studies in Newham and the Isle of Wight.	Infection rates grew approximately exponentially.
Deployment	1 Oct 2020 - 7 Oct 2020	The number of app users increased rapidly in the first week after launch (24-30 Sep). This phase is excluded from our statistical analysis (which assumes a steady-state number of users) but not from our modelling approach.	
1	8 Oct 2020 - 6 Nov 2020	The phase begins with stabilisation of number of app users (around 30 Sep), and ends with release of version 3.9 of the app (29 Oct). During this phase the app used a simple implementation of GAEN with a conservative (high) threshold for triggering exposure notifications.	Local alert levels (3-tier system) in England from 14 Oct. Firebreak lockdown in Wales 23 Oct - 9 Nov.
2	7 Nov 2020 - 31 Dec 2020	The phase begins with release of version 3.9 of the app (29 Oct), when a custom risk scoring system for exposure notification was introduced in England and Wales and the number of notifications per index case increased immediately by a factor of 2. The phase ends when the threshold risk score for exposure notification was reduced (Dec 23), leading to a further immediate increase in the number of notifications.	England lockdown until 2 Dec, 3-tier system afterwards. Emergence of the new B.1.1.7 viral variant. Tier 4 introduced on 20 Dec.
3	1 Jan 2021 onwards	The phase begins with the change in threshold risk score (Dec 23). We exclude this phase from our analysis, because the app was sufficiently different from phase 2 to be separate, but there were not enough data for reliable analysis. The start of an extended national lockdown on 4 January further complicates interpretation of data.	
App (1 & 2 combined)	8 Oct 2020 - 31 Dec 2020	Combined period for the overall effect of the app, at the present time of analysis	

Phases are justified in terms of changes to the NHS COVID-19 App. *Changes in case numbers resulting from changes to the app will lag behind in time; we assumed by 8 days, hence for example the change in the app occurring on 23 December is not expected to be reflected in case numbers until 31 December.

Extended Data Table 2 | Coefficients for the main regression

Phase	Coefficient	Estimate	95% confidence interval	P value
0 (placebo)	beta_rural_urban	0.054	0.030 - 0.079	2e-5
	beta_gdp_band	0.0097	0.0005 - 0.019	0.038
	beta_poverty	0.039	0.026 - 0.052	1e-8
	beta_users*	-0.0062	-0.016 - 0.0041	0.24
1	beta_rural_urban	0.078	0.052 - 0.10	6e-9
	beta_gdp_band	0.0060	-0.0035 - 0.016	0.21
	beta_poverty	0.021	0.0076 - 0.034	0.002
	beta_users*	-0.011	-0.022 - -0.0003	0.04
2	beta_rural_urban	0.063	0.041 - 0.085	5e-8
	beta_gdp_band	-0.0002	-0.0083 - 0.0078	0.95
	beta_poverty	-0.0098	-0.021 - 0.0018	0.09
	beta_users*	-0.027	-0.036 - -0.018	4e-8
1 and 2 combined	beta_rural_urban	0.070	0.052 - 0.088	1e-12
	beta_gdp_band	-0.00096	-0.0078 - 0.0059	0.79
	beta_poverty	0.002	-0.0076 - 0.012	0.68
	beta_users*	-0.023	-0.030 - -0.015	1e-8

P values are for the regression coefficients being non-zero, with a two-sided t test unadjusted for multiple tests. *when beta_users is negative, its absolute value is the decrease in log(cases) per 1% increase in app users.

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Extended Data Table 3 | Regression results for the matched pairs analysis

Phase	Coefficient	Estimate	95% confidence interval	P value
0 (placebo)	beta_rural_urban	-0.0033	-0.014 - 0.07	0.51
	beta_gdp_band	-0.002	-0.0059 - 0.002	0.32
	beta_poverty	0.0011	-0.039 - 0.006	0.65
	beta_users*	0.0002	-0.0045 - 0.0049	0.93
1	beta_rural_urban	0.014	-0.059 - 0.087	0.7
	beta_gdp_band	0.002	-0.026 - 0.03	0.89
	beta_poverty	-0.013	-0.049 - 0.022	0.46
	beta_users*	-0.051	-0.084 - -0.018	0.004
2	beta_rural_urban	0.016	-0.046 - 0.078	0.61
	beta_gdp_band	0.004	-0.02 - 0.028	0.73
	beta_poverty	-0.005	-0.036 - 0.025	0.72
	beta_users*	-0.039	-0.067 - -0.01	0.009
1 and 2 combined	beta_rural_urban	0.016	-0.043 - 0.075	0.59
	beta_gdp_band	0.002	-0.021 - 0.025	0.86
	beta_poverty	-0.0047	-0.033 - 0.024	0.74
	beta_users*	-0.044	-0.071 - -0.017	0.0023

P values are for the regression coefficients being non-zero, with a two-sided t test unadjusted for multiple tests. *when beta_users is negative, its absolute value is the decrease in log(cases) per 1% increase in app users.

Extended Data Table 4 | Results for regression adjusting for quality of manual contact tracing

Phase	Coefficient	Estimate	95% confidence interval	P value
0	beta_rural_urban	-0.0096	-0.025 - 0.056	0.20
	beta_gdp_band	-0.0024	-0.0068 - 0.002	0.28
	beta_poverty	0.0032	-0.0016 - 0.008	0.18
	beta_manual_tracing*	-0.003	-0.0067 - 0.00063	0.10
	beta_users*	0.0005	-0.0043 - 0.0052	0.84
1	beta_rural_urban	0.036	-0.088 - 0.16	0.55
	beta_gdp_band	0.0037	-0.032 - 0.04	0.83
	beta_poverty	0.0018	-0.037 - 0.04	0.92
	beta_manual_tracing*	-0.037	-0.067 - -0.0072	0.018
	beta_users*	-0.047	-0.085 - -0.0079	0.021
2	beta_rural_urban	0.018	-0.09 - 0.13	0.73
	beta_gdp_band	0.0057	-0.026 - 0.037	0.71
	beta_poverty	0.0017	-0.036 - 0.032	0.92
	beta_manual_tracing*	0.008	-0.018 - 0.034	0.53
	beta_users*	-0.028	-0.062 - 0.0064	0.11
1 and 2 combined	beta_rural_urban	0.023	-0.084 - 0.13	0.66
	beta_gdp_band	0.0037	-0.027 - 0.035	0.8
	beta_poverty	0.0024	-0.031 - 0.036	0.88
	beta_manual_tracing*	-0.0057	-0.031 - 0.02	0.65
	beta_users*	-0.035	-0.068 - -0.0016	0.041

P values are for the regression coefficients being non-zero, with a two-sided t test unadjusted for multiple tests. *when beta_users and beta_manual_tracing are negative, their absolute values are the decrease in log(cases) per 1% increase in app users and per 1% increase in contacts reached, respectively.

Corresponding author(s): Christophe Fraser

Last updated by author(s): Apr 20, 2021

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Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection

Data was gathered by the COVID-19 NHS app team on behalf of the Department of Health and Social Care of the United Kingdom and made available to the authors for this analysis.

Data analysis

Raw data was extracted from the database using Python (version 3.8) code. The analysis was performed with custom R (version 4.0.2) code, openly available on GitHub at https://github.com/BDI-pathogens/nhs_covid_app_evaluation for evaluation.

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- Accession codes, unique identifiers, or web links for publicly available datasets
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Data access is managed by the DHSC. An application is underway to make all data necessary to reproduce our analyses available to accredited researchers through the Office for National Statistics <https://www.ons.gov.uk/aboutus/whatwedo/statistics/requestingstatistics/approvedresearcherscheme>. Data aggregated spatially and temporally is available initially at <https://faq.covid19.nhs.uk/article/KA-01367/en-us>, and eventually at <https://stats.app.covid19.nhs.uk/>.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	All available data - gathered in the database of the NHS COVID-19 app - was used.
Data exclusions	None.
Replication	Not relevant: this was an observational study.
Randomization	We adjusted for multiple confounding variables and performed a placebo regression to verify removal of one measure of non-causal correlation (anachronistic association between cause and effect).
Blinding	The treated units were effectively blinded to the dose of their treatment: inhabitants of each geographical unit were not informed of the fraction of their local population who were using the app. Investigators were not blinded to the treatment dose: the quantity we studied was how the response (number of COVID-19 cases) changed with continuously varying treatment dose (i.e. not a discrete comparison of treated vs untreated), and so knowledge of the treatment dose was necessary. Investigator knowledge of the treatment dose could not have affected the treatment's true effect because this was a retrospective observational study. This can be contrasted with the possible bias, for example, from health care workers knowing they are providing either a placebo or a treatment at the moment of provision.

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