Mental health in UK Biobank – development, implementation and results from an online questionnaire completed by 157 366 participants: a reanalysis*


Background
UK Biobank is a well-characterised cohort of over 500 000 participants including genetics, environmental data and imaging. An online mental health questionnaire was designed for UK Biobank participants to expand its potential.

Aims
Describe the development, implementation and results of this questionnaire.

Method
An expert working group designed the questionnaire, using established measures where possible, and consulting a patient group. Operational criteria were agreed for defining likely disorder and risk states, including lifetime depression, manic/hypomanic, generalised anxiety disorder, unusual experiences and=self-harm, and current post-traumatic stress and hazardous/harmful alcohol use.

Results
A total of 157 366 completed online questionnaires were available by August 2017. Participants were aged 45–82 (53% were ≥65 years) and 57% women. Comparison of self-reported diagnosed mental disorder with a contemporary study shows a similar prevalence, despite respondents being of higher average socioeconomic status. Lifetime depression was a common finding, with 24% (37 434) of participants meeting criteria and current hazardous/harmful alcohol use criteria were met by 21% (32 602), whereas other criteria were met by less than 8% of the participants. There was extensive comorbidity among the syndromes. Mental disorders were associated with a high neuroticism score, adverse life events and long-term illness; addiction and bipolar affective disorder in particular were associated with measures of deprivation.

Conclusions
The UK Biobank questionnaire represents a very large mental health survey in itself, and the results presented here show high face validity, although caution is needed because of selection bias. Built into UK Biobank, these data intersect with other health data to offer unparalleled potential for crosscutting biomedical research involving mental health.

Declaration of interest
G.B. reports grants from the National Institute for Health Research during the conduct of the study; support from Illumina Ltd and the European Commission outside the submitted work. B.C. reports grants from the Scottish Executive Chief Scientist Office during the conduct of the study. C.S. reports grants from the Medical Research Council and Wellcome Trust, during the conduct of the study; and is the former Chief Scientist for UK Biobank. M.H. reports grants for IMI RADAR-CNS and personal fees as an expert witness outside the submitted work. N.A. is Chief Scientist for UK Biobank. Other authors have nothing to declare.

Keywords
Mental health; UK Biobank; cohort study; depressive disorders; alcohol disorders.

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UK Biobank
UK Biobank is a very large, population-based cohort study established to identify the determinants of common life-threatening and disabling conditions.† Most of these conditions, such as heart disease, stroke and mental disorders, are multifactorial, involving multiple genes of small effect, and complex relationships with environmental exposures. This means large samples are required to study associations between these exposures and disease, and to identify targets for treatment and prevention.‡ The utility of traditional epidemiological study designs are often limited by their focus on single disorders or exposures and relatively modest sample sizes.§ UK Biobank is an open-access resource providing detailed characterisation of over 150 million people aged 40–69 years at recruitment, with proposed long-term follow-up. Recruitment was completed in 2010, along with consent for future contact and linkage to routinely collected health-related data, such as those produced by the National Health Service (NHS). Baseline measures were extensive, from family history to sensory acuity (a searchable breakdown is available at www.ukbiobank.ac.uk), and the resource continues to grow. In 2017 genotyping of the whole cohort was complete, a range of blood biomarkers were released in 2019, and multimodal imaging is underway for 100 000 participants.¶ Locality environmental factors, such as air pollution, are also available. The design of UK Biobank offers the opportunity to examine a wide range of

risk factors and outcomes in a sample that has the size to provide the power to detect small effects, making UK Biobank a highly efficient resource for observational epidemiology.

The impact of mental disorders on disability and quality of life is considerable, accounting for the equivalent of over 1.2 million person-years lost to disability from mental and substance-use disorders in England alone in 2013. The detrimental impact of mental disorders both on physical disease onset and outcomes is particularly notable for this project. The UK Biobank baseline data collection of mental health, consisted of several questions about mood and a neuroticism scale, expanded for the last 172,729 recruited participants with questions to allow provisional categorisation of mood disorder, however, there was considerable scope for further characterisation of mental disorders among participants. The availability of mental health phenotypes in conjunction with the wealth of other data in the UK Biobank offers considerable opportunities to study aetiological and prognostic factors, particularly the interplay between factors that have usually been in separate research domains.

Outcome ascertainment

Characterising mental disorders in a cohort such as UK Biobank poses challenges. First, most mental disorders manifest before age 30 years and have fluctuating courses, so a ‘snapshot’ of disorder status at one point in time, as identified by most screening tools, is likely to be less useful than a ‘lifetime’ history – although ‘lifetime’ instruments suffer more from measurement error such as recall bias. Second, traditional diagnostic approaches to mental disorders, relying upon clinician assessment at interview, would be prohibitively expensive in a cohort of this size. Third, using self-report of diagnosis or data from record linkages relies upon recognition of illness and reflects healthcare usage patterns, whereas many people with mental disorders never seek or receive treatment. In response to these challenges, we developed a dual approach: secondary care record linkage for identification of more severe illnesses such as schizophrenia and self-report of symptoms of common mental disorder, which might not have come to clinical attention. As part of our mental health phenotyping programme we therefore developed an online mental health questionnaire (MHQ) for participants to complete regarding lifetime symptoms of mental disorders. The MHQ aimed to exploit the efficiency of ‘e-surveys’ and provide the detail needed to identify mental health disorders without the need for a clinical assessment.

Aims

The present paper aims to describe the development, implementation and results of the MHQ. We provide descriptive data on the numbers of UK Biobank participants meeting diagnostic criteria for specific disorders and on the frequency of exposure to risk factors. We also evaluate the likely representativeness of respondents by comparing respondent sociodemographic characteristics to that of the UK population using census data and comparing self-reported mental disorder diagnosis with the Health Survey for England (HSE) data. This will assist researchers considering or undertaking epidemiological research to evaluate the potential strengths and weaknesses of using UK Biobank data to look at mental health.

Method

Questionnaire development

A mental health research reference group formed of approximately 50 individuals (see supplementary Appendix 1 available at https://doi.org/10.1192/bjo.2019.100) participated in discussions about a strategy for mental health phenotyping in UK Biobank, including a workshop in January 2015. From this, a smaller steering group was established and led the development of the MHQ. The group recommended that the MHQ should concentrate on depression, as it was likely to represent the greatest burden in the cohort, with some questions about other common disorders, including anxiety, alcohol misuse and addiction, plus risk factors for mental disorders not captured at participants’ baseline assessment.

The intention was to create a composite questionnaire out of previously existing and validated measures, taking into account participant acceptability (time, ease of use and ensuring questions were unlikely to offend), scope for collaborations with international studies (for example the Psychiatric Genomics Consortium) through making results comparable, and the need to balance depth and breadth of phenotyping. The base of the questionnaire was the measurement of lifetime depressive disorder using the Composite International Diagnostic Interview Short Form (CIDI-SF), modified to provide lifetime history, as used to identify cases and controls for some existing studies in the Psychiatric Genomics Consortium. The CIDI-SF uses a branching structure with screening questions and skip rules to limit detailed questions to the relevant areas for each participant. Other measures were then added to this, as summarised in supplementary Table SM1. Where the group were unable to find existing measures that fulfilled these criteria, questions were written or adapted, as indicated in supplementary Table SM1. These sections have not been externally validated, but the questions along with the full questionnaire can be seen on the UK Biobank website (http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=22), for researchers to evaluate.

Testing and ethical approval

The use of branching questions in the MHQ means that those with established and multiple mental disorders have a longer, more detailed, questionnaire. To improve acceptability in this group, we worked with a patient advisory group at the National Institute of Health Research (NIHR) Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust in designing the questionnaire and invitation. We then piloted the questionnaire for functionality (for example ease of completion) among an online cohort of 14,836 volunteers aged over 50 and living in the UK, who completed the questionnaire as part of signing up to take part in the Platform for Research Online to investigate Genetics and Cognition in Ageing (PROTECT). Of those who started the questionnaire 98.8% completed it, taking a median time of 15 min. Some PROTECT participants commented that they wanted the opportunity to explain why they felt they had experienced symptoms of depression. In response to this, we added a question to the depression section on loss or bereavement, and a free-text box – neither were designed to change diagnostic algorithms, but may add to future analyses.

The questionnaire was approved as a substantial amendment to UK Biobank approval from the North West - Haydock Research Ethics Committee, 11/NW/0382. Participation in the UK Biobank is voluntary, and participants are free to withdraw at any time. Informed written consent was obtained by participants at baseline. Online questionnaires such as the MHQ are voluntary.

Administration to UK Biobank participants

We incorporated the final MHQ into the UK Biobank web-questionnaire platform and presented it to participants as an online questionnaire entitled ‘thoughts and feelings’. To participants who had agreed to email contact (339,092/503,328 participants, 67%) we sent a hyperlink to their personalised questionnaire. The
the purpose of reproducing these analyses or developing further analyses (https://data.mendeley.com/datasets/kv677c2thv/3). We used R version 3.4.0–3.5.1 and MS Excel for analyses. We report numbers and proportions within the sample and do not attempt to give population prevalence estimates. Because of this, and the large sample size (the 95% CIs on all proportions have width of less than absolute 1%), CIs were thought not to add meaning, and so are not shown. A STrengthening the Reporting of OBservational studies in Epidemiology checklist is included in supplementary Appendix 3.

Comparison data

In order to describe the differences in the sample of participants in UK Biobank to the general population of the UK, Fry et al24 compare UK Biobank data with census data, which we have replicated and extended. For health-related data, we have used the Health Survey for England (HSE), which is a face-to-face household survey carried out every year25 that in 2014 involved around 8000 adult participants designed to be representative of the England adult population (with weighting in cases where sampling could not achieve this). Some topics are ‘core’ and are surveyed every year, whereas others are ‘supplementary’. Mental health appeared in the 2014 survey as a supplementary topic.17

Results

The setting, recruitment and methods of selection of participants in UK Biobank have been published elsewhere.1,4,10 For the MHQ study, 339 092 participants were sent an email invitation, and 157 366 (46% of those emailed) fully completed the questionnaire by July 2017 (available in August 2017) – which means that the MHQ had 31% coverage of the UK Biobank cohort. The coverage continues to grow as the questionnaire is still open for participants. Figure 1 shows the flow chart of UK Biobank participants who completed the MHQ. The median time for completion was 14 min, and 82% of respondents completed the questionnaire in under 25 min.

Supplementary Table SM2 shows participant characteristics for all UK Biobank participants and those who completed the MHQ compared with population-level data for UK residents in the same age range. The MHQ participants were aged 45–82 years, with 53% aged 65 or over, and 57% were female. They were different from the whole UK Biobank cohort and the general population by being better educated (for example 45% hold a degree v. 32% of all UK Biobank participants v. 23% in the census), of higher socioeconomic status according to job type, and healthier (28% report long-standing illness or disability v. 32% all UK Biobank participants v. 37% census), with lower rates of current smoking.

Table 1 shows that 34% of respondents reported they had received at least one psychiatric diagnosis from a professional at some time, and 12% had received two or more. The most commonly reported diagnosis was depression, followed by ‘anxiety or nerves’. Data are compared with the population prevalence estimates from HSE for this age group.17 The comparison shows that the pattern and prevalence of diagnosis are similar; for example, a depression diagnosis was self-reported by 21% of individuals in both samples, eating disorder by around 1% and bipolar-related disorders by around 0.5%. The definition in the MHQ differed from that in the HSE for anxiety (the MHQ definition was broader) and addiction (MHQ did not require professional diagnosis), and the higher overall prevalence in the UK Biobank MHQ compared with the HSE (34.3% v. 28.0%) may be a result of those wider definitions.

Table 2 shows that 45% of participants met criteria for one or more operationally defined syndromes. Of the lifetime disorders, depression was most common (24% respondents participants),
then GAD (7%) and hypomania/mania (2%); current hazardous/harmful alcohol use was met by 21% and current PTSD by 6%. Lifetime unusual experiences were reported by 5% of respondents and self-harm by 4%. Supplementary Table SM3 shows that women and men were approximately equally likely to have a history of one or more of the defined syndromes (women 44% v. men 46%), but differed as to which criteria were met: women were more likely to have a history of depression or anxiety disorder, whereas men were more likely to meet criteria for a current hazardous/harmful alcohol use (women 14% v. men 30%). Table 2 also shows the substantial comorbidity of defined syndromes. Notably, around three-quarters of participants who met criteria for lifetime anxiety disorder also met criteria for lifetime depression. Also, although individuals meeting criteria for PTSD had more than a twofold risk of all of the lifetime syndromes compared with average, those identified with hazardous/harmful alcohol use had little extra risk of lifetime syndromes.

In Table 3, people meeting criteria for the lifetime occurrence of at least one of depression, bipolar disorder, GAD, unusual experiences or self-reported addiction are seen to be more likely than those without to come from a younger age group, report adverse life events and have met criteria for loneliness or social isolation. They are more likely to have smoked cigarettes and/or used cannabis, and to have had a ‘longstanding illness’ at baseline (although the presence of a mental disorder may have been the illness to which the participants refer in some cases), but all groups were equally likely to be achieving recommended levels of physical activity. Markers of deprivation (area-level deprivation and rented housing) are raised in groups with a history of mental disorders, especially bipolar affective disorder and addictions.

The supplementary material includes a section on mood disorder, showing the results of analyses of MHQ participants by likely disorder categories (supplementary Fig. MD1). Supplementary Table MD1 shows the features of these groups. The characteristics of people who meet diagnostic criteria for depression appear to be shared by those with subthreshold depressive symptoms. Supplementary Table MD2 shows comorbidity, and demonstrates a gradient effect in the presence of a non-depression syndrome rising from 23% in no depression (mainly hazardous/harmful alcohol use) to 50% in recurrent depression. Supplementary Table MD3 shows that people with a history of depression or bipolar affective disorder tend to have worse scores for current mental health.

Discussion

Main findings relating to data-collection methods

This paper has described the development, implementation and principal descriptive findings from the UK Biobank MHQ. The implementation of this questionnaire demonstrates that a web-based questionnaire is an acceptable means of collecting mental health information at low cost and large scale. Although the data-collection methods might force more limited data acquisition than conventional interview methods, with associated uncertainties in true diagnostic categorisation, we suggest that the survey achieved an acceptable trade-off between depth of phenotypic information and scale of sample size. This means that the UK Biobank MHQ sample can usefully fill a gap between clinical samples with detailed mental health disorder information but poor generalisability (for example, Clinical Records Interactive Search) and larger
Main findings from the questionnaire

Those who completed the MHQ appear to be better educated and have higher socioeconomic status (job title, household income, home ownership and area-level deprivation) than those recruited into UK Biobank overall, and the UK population. Despite this, we found that rates of self-report diagnoses were similar to population cohorts with superficial identification of mental disorder (such as the baseline UK Biobank cohort or 23andMeD2).
estimates from the HSE. The patterns of association between disorders and demographics were also broadly as predicted by previous research, which adds to the face validity of the questionnaire. For example, depression and anxiety were more common in women, whereas addiction and alcohol misuse were more common in men, and all disorders were less common in responders older than 65 years. The decrease in prevalence of lifetime disorder with increasing age has been previously noted in cross-sectional studies, although the causes and implications are not clearly understood.36,37 The high level of hazardous/harmful alcohol (using the Alcohol Use Disorder Identification Tool) is consistent with the established literature, supporting the use of the data to study the relationships between exposures and outcomes. Previous work on health surveys with selection bias because of non-participation, including UK Biobank, have indicated that they can be used to give estimates of association,14,32,35 although biased results may occur in some cases.36,37 For example, the relative under-participation of unskilled workers in the MHQ (around one-fifth of the proportion in the population) could mask an association with a variable that was related to unskilled work.

Table 3: Selected personal characteristics, socioeconomic factors, risk factors and health behaviours by status for likely lifetime occurrence of operationally defined syndromes (people may be included in more than one category)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No ‘lifetime’ criteria metb (n = 108 752)</th>
<th>Depressionb (n = 37 434)</th>
<th>Bipolar type 1c (n = 931)</th>
<th>Anxiety disorder (GAD)d (n = 11 111)</th>
<th>Unusual experiencesd (n = 7 803)</th>
<th>Addictione (n = 9 386)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal features</td>
<td>Age, n (%)</td>
<td>45–54</td>
<td>14 364 (13)</td>
<td>7145 (19)</td>
<td>228 (24)</td>
<td>2348 (21)</td>
</tr>
<tr>
<td></td>
<td>55–64</td>
<td>33 307 (31)</td>
<td>14 809 (48)</td>
<td>417 (45)</td>
<td>4470 (40)</td>
<td>2904 (37)</td>
</tr>
<tr>
<td></td>
<td>65–74</td>
<td>51 706 (48)</td>
<td>13 739 (37)</td>
<td>261 (28)</td>
<td>3892 (35)</td>
<td>2960 (38)</td>
</tr>
<tr>
<td></td>
<td>≥75 (oldest is 82)</td>
<td>9376 (9)</td>
<td>1741 (5)</td>
<td>25 (3)</td>
<td>401 (4)</td>
<td>454 (6)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Female</td>
<td>57 556 (53)</td>
<td>25 815 (69)</td>
<td>532 (57)</td>
<td>7404 (67)</td>
<td>4718 (60)</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>105 072 (97)</td>
<td>36 297 (97)</td>
<td>892 (96)</td>
<td>10 749 (97)</td>
<td>7503 (96)</td>
</tr>
<tr>
<td>Townsend Deprivation Score,e (%)</td>
<td>Most deprived (TDS ≥2)</td>
<td>11 783 (11)</td>
<td>5656 (15)</td>
<td>201 (22)</td>
<td>1855 (17)</td>
<td>1426 (18)</td>
</tr>
<tr>
<td>Highest qualification, n (%)</td>
<td>Degree</td>
<td>48 700 (45)</td>
<td>16 939 (45)</td>
<td>425 (46)</td>
<td>5071 (46)</td>
<td>3646 (47)</td>
</tr>
<tr>
<td>Housing tenure, n (%)</td>
<td>Rentf</td>
<td>4162 (4)</td>
<td>2906 (8)</td>
<td>155 (17)</td>
<td>1026 (9)</td>
<td>854 (11)</td>
</tr>
<tr>
<td>Known risk factors</td>
<td>Neuroticism score,g mean (s.d.)</td>
<td>3.2 (2.8)</td>
<td>5.6 (3.3)</td>
<td>3.8 (3.1)</td>
<td>7.1 (3.3)</td>
<td>5.2 (3.5)</td>
</tr>
<tr>
<td></td>
<td>Adverse life experiences, n (%)</td>
<td>Childhood screenh</td>
<td>43 913 (42)</td>
<td>21 144 (54)</td>
<td>638 (69)</td>
<td>6971 (62)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult screeni</td>
<td>50 226 (46)</td>
<td>23 892 (64)</td>
<td>685 (74)</td>
<td>7981 (68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma exposurej</td>
<td>50 771 (47)</td>
<td>22 166 (59)</td>
<td>665 (71)</td>
<td>6877 (62)</td>
</tr>
<tr>
<td></td>
<td>Social connection, n (%)</td>
<td>Lonelinessk (≥3)</td>
<td>2976 (3)</td>
<td>2367 (6)</td>
<td>94 (10)</td>
<td>971 (9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Social isolationl</td>
<td>7793 (7)</td>
<td>3827 (10)</td>
<td>126 (14)</td>
<td>1173 (11)</td>
</tr>
<tr>
<td></td>
<td>Illness</td>
<td>Longstanding illness, disability or infirmitym</td>
<td>26 341 (24)</td>
<td>13 363 (36)</td>
<td>503 (54)</td>
<td>4581 (41)</td>
</tr>
<tr>
<td>Health behaviours</td>
<td>Smoking status,n (%)</td>
<td>Current</td>
<td>6235 (6)</td>
<td>3638 (10)</td>
<td>158 (17)</td>
<td>1194 (11)</td>
</tr>
<tr>
<td></td>
<td>Cannabis use (lifetime), n (%)</td>
<td>Daily</td>
<td>888 (1)</td>
<td>914 (2)</td>
<td>63 (7)</td>
<td>346 (3)</td>
</tr>
<tr>
<td></td>
<td>Physical activity,n (%)</td>
<td>Moderate activity ≥ three times a week</td>
<td>39 677 (36)</td>
<td>13 988 (37)</td>
<td>345 (37)</td>
<td>4174 (38)</td>
</tr>
</tbody>
</table>

a. Criteria not met for depression, generalised anxiety disorder (GAD), unusual experiences or addiction.
b. Criteria met for disorder on Composite International Diagnostic Interview Short Form (CIDIS SF) lifetime.
c. Criteria met for both lifetime depression and lifetime mania.
d. Reported potential hallucination or delusion at any point in their life.
e. Positive endorsed: “have you been addicted to or dependent on one or more things, including substances (not cigarettes/coffee) or behaviours (such as gambling)”?
f. Age when mental health questionnaire completed, derived from date of birth.
g. Townsend Material Deprivation Score is based on postcode areas.
h. Includes rent social and rent private, excludes other categories of housing tenure.
i. Age when mental health questionnaire completed, derived from date of birth.
j. Reported potential hallucination or delusion at any point in their life.
k. Criteria met for both lifetime depression and lifetime mania.
l. Positive endorsed: “have you been addicted to or dependent on one or more things, including substances (not cigarettes/coffee) or behaviours (such as gambling)”?
m. Age when mental health questionnaire completed, derived from date of birth.

‘Healthy volunteer’ selection bias

The ‘healthy volunteer’ selection bias within the UK Biobank has been previously explored,38 and further variables influencing participation in the MHQ can be predicted and have been found, such as interest in mental health and good cognition.39 The impact of selection biases on disease prevalence are likely to be particularly strong for mental health disorders, where disorder status or symptoms may influence participation in research,12,33 and many risk factors for these disorders, including genetic risk, can be associated with non-participation.34 Therefore, the results of the MHQ should not be used to provide prevalence estimates. However, the pattern of the measured risk factors among the participants with mental disorders in the MHQ, including neuroticism, trauma, loneliness and housing tenure, was in accordance with established literature, supporting the use of the data to study the relationships between exposures and outcomes. Previous work on health surveys with selection bias because of non-participation, including UK Biobank, have indicated that they can be used to give estimates of association,14,32,35 although biased results may occur in some cases.36,37 For example, the relative under-participation of unskilled workers in the MHQ (around one-fifth of the proportion in the population) could mask an association with a variable that was related to unskilled work.

Strengths and limitations

We developed a questionnaire through a consensus approach with clear aims of capturing enough data to characterise participants as having a lifetime history of depression and other phenotypes. Validated instruments were used where possible. The consortium working on the questionnaire included mental health researchers and members of the UK Biobank team working in collaboration to develop the optimum approach. The derived variables of likely categorical diagnoses will be added to the UK Biobank resource, facilitating those less familiar with mental health to use the results.
In conclusion, UK Biobank offers a unique opportunity to research common disorders in a well-characterised longitudinal cohort of UK adults. A detailed MHQ has now been completed by 157,366 UK adults. A detailed MHQ has now been completed by 157,366 UK adults. A detailed MHQ has now been completed by 157,366 UK adults. In conclusion, UK Biobank offers a unique opportunity to research common disorders in a well-characterised longitudinal cohort of UK adults. A detailed MHQ has now been completed by 157,366 UK adults. A detailed MHQ has now been completed by 157,366 UK adults.

Implications

In UK Biobank, mental health information includes validated ratings from Hospital Episode Statistics for mental health diagnoses, incorporation of general practice records, triangulation of health record and questionnaire data, and investigation of further putative phenotypes. UK Biobank mental health data can be seen in a searchable database of approved research.

This study also demonstrates the substantial burden of mental health disorders, including potentially dangerous patterns of alcohol consumption. Given the known impact of mental health on physical health, mental health data and its associations should interest researchers from every biomedical specialty. This study suggests that UK Biobank could be a powerful tool for such studies, and as it is open to all bona fide health researchers for work in the public good, we hope this study will inspire both existing and new users of UK Biobank.
of the questionnaire. G.B. and J.R.C. curated data. K.A.S.D., J.R.C., M.A., B.C., C.D., N.G., W.L., R.P., D.S., and J.W. contributed to analysis. K.A.S.D., J.R.C. and M.H. wrote the paper. All authors critically edited the paper. All authors agreed to submission.

Supplementary material
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References