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1

2 i)

3 Indicators of Mental Disorders in UK Biobank – A comparison of
4 approaches

5

6 ii)

7 Indicators of Mental Disorders in UK Biobank

8 iii)

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24

25

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52 We have read and understood the author guidelines of ethical conduct and wish to declare the
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58

60 vii)Abstract

61 Objectives: For many research cohorts, it is not practical to provide a "gold-standard"
62 mental health diagnosis. It is therefore important for mental health research that
63 potential alternative measures for ascertaining mental disorder status are understood.

64 Methods: Data from UK Biobank in those participants who had completed the online
65 Mental Health Questionnaire (n=157,363) were used to compare the classification of
66 mental disorder by four methods: symptom-based outcome (self-complete based on
67 diagnostic interviews), self-reported diagnosis, hospital data-linkage and self-report
68 medication.

69 Results: Participants self-reporting any psychiatric diagnosis had elevated risk of any
70 symptom-based outcome. Cohen's kappa between self-reported diagnosis and
71 symptom-based outcome was 0.46 for depression, 0.28 for bipolar affective disorder,
72 and 0.24 for anxiety. There were small numbers of participants uniquely identified by
73 hospital data-linkage and medication.

74 Conclusion: Our results confirm that ascertainment of mental disorder diagnosis in large
75 cohorts such as UK Biobank is complex. There may not be one method of classification
76 that is right for all circumstances, but an informed and transparent use of outcome
77 measure(s) to suit each research question will maximise the potential of UK Biobank and
78 other resources for mental health research.

79

80 keywords: cohort study, online survey, mental disorder, epidemiology, diagnosis, UK
81 Biobank

82 viii)

83 **Introduction**

84 Mental health is a major, and growing, contributor to disability worldwide (Whiteford, Ferrari,
85 Degenhardt, Feigin, & Vos, 2015), prompting the need to take advantage of all available resources in
86 order to progress the understanding of mental disorders and the interplay between mental and
87 physical health (Prince et al., 2007). To this end, it is necessary to describe mental disorders and
88 related traits in large-scale epidemiological studies. The use of self-report diagnosis, administrative
89 data and on-line surveys are potential sources of data on mental disorders that may be of use in this
90 context, and so it is important to understand the advantages and limitations of these measures.

91

92 **Considerations Regarding Indicators of Mental Health**

93 Mental disorder diagnosis is a complex specialist task, requiring elucidation of symptoms, time-
94 course, and context (Casey & Kelly, 2007). It has not yet been possible to categorise mental disorders
95 using pathology or etiology, so, in order that there can be a common language, they have been
96 systematised into syndromes based on signs and symptoms (Clark, Cuthbert, Lewis-Fernández,
97 Narrow, & Reed, 2017). However, it is not clear to what extent these syndromes reflect true disease
98 entities, leaving difficulties at the boundaries both from normal variation, and between different
99 disorders (Kendell & Jablensky, 2003). Mental health research traditionally relies on lengthy
100 structured or semi-structured interviews to provide a “gold standard” highly reproducible syndromic
101 diagnosis (Haro et al., 2006; Rucker et al., 2011), but these are costly to administer, placing a limit on
102 sample sizes.

103

104 Common sources of mental disorder status in studies with large sample sizes are symptom scales or
105 check-lists, self-reported clinical diagnoses and medication, and registries. Self-report can be
106 captured in a traditional interview, or using novel forms, such as online questionnaires, which vastly
107 decrease costs of acquiring information (Andersson, Ritterband, & Carlbring, 2008). Registry data no
108 longer comes only from databases set up specifically for research, but can be derived from
109 administrative data. Data-linkage to these sources offers benefits of a wider range of reports
110 without the direct costs of acquiring data, but raises problems of interpreting and validating those
111 reports (Stewart & Davis, 2016).

112

113 Clinician diagnoses derived from self-reported or data-linkage, should reflect the outcome of a
114 nuanced clinical assessment, but those people who have received a diagnosis are those who have
115 accessed services, whereas a large proportion of people with a mental disorder are never formally

116 identified as such (Goldberg & Huxley, 1980). Passage into healthcare will depend upon the type and
117 severity of illness, and patient factors; receiving a diagnosis and treatment depends additionally on
118 clinician and service factors. Such factors are vulnerable to age and cohort effects. For example,
119 antidepressant treatment for those in whom the survey found symptoms of a common mental
120 disorder in the previous year was almost three times more likely in 2009 (15.9%) than it had been in
121 1993 (5.7%) (Spiers et al., 2016).

122

123 A retrospective enquiry adds recall bias for both symptoms and diagnoses. One study estimated that
124 ability to recall a period of sadness likely to represent depression fell from 90% if it occurred in the
125 last year to 41% if it occurred ten years ago (Patten et al., 2012). This problem is not confined to
126 mental health, since self-report of clinician diagnosis of physical disorders including heart failure and
127 previous cancer can be unreliable, leading mostly to under ascertainment (Nord, Mykletun, & Fosså,
128 2003; Okura, Urban, Mahoney, Jacobsen, & Rodeheffer, 2004). It may be that mental disorders are
129 also under-reported due to perceived stigma of the disorder (Nevin, 2009; Simon & VonKorff, 1995).

130

131 **Comparison of Approaches in One Resource**

132 UK Biobank (UKB) is a research cohort for which over 503,328 people aged 49-60 enrolled in 2007-
133 2010. This involved questionnaires, biosamples, and consent for linkage of routinely collected
134 healthcare data and to take part in further waves of data collection (Sudlow et al., 2015).

135

136 The Mental Health Outcome Consortium was formed to develop mental health phenotyping in UKB.
137 Mental disorder in this context might be both an outcome and a risk factor for other health
138 outcomes. The consortium has focussed on two aspects: validating administrative secondary care
139 diagnostic codes (Davis, Bashford, et al., 2018; Davis, Sudlow, & Hotopf, 2016); and designing an
140 online mental health questionnaire (MHQ) to identify symptom-based outcomes (Davis, Coleman, et
141 al., 2018). Some of the outcomes in the MHQ are based on diagnostic interviews and are analogous
142 to mental disorder diagnoses (e.g. depression and generalised anxiety disorder). Others assess other
143 aspects of mental health such as psychotic experiences (PE) and self-harm. Results of the UKB MHQ
144 are available for 157,366 participants, representing 31% of the original UKB sample (Davis, Coleman,
145 et al., 2018).

146

147 UKB now provides multiple indicators that could be used as a means to identify mental disorders,
148 none of which represents a "gold-standard" diagnosis against which the others can be validated. This
149 could lead to confusion and dilemmas as to which measure to use for research. Although there have

150 been studies that compare individual measures against a conventional gold standard, there are few
151 resources that help guide the choice of imperfect measures in large studies such as UKB. The aim of
152 this study is to compare four indicators of mental health and disorder in UKB for multiple outcomes,
153 in order to guide future research in UKB and the design of similar studies.

154 Methods

155 UKB is a major open science resource (Sudlow et al., 2015). Extensive data is already available on the
156 503,328 volunteers in UKB (UK Biobank, 2018), who responded to invitations sent by mail to people
157 aged 40-69 who lived near to 22 assessment centres in England, Scotland and Wales. The
158 composition has been documented, and it has been noted that the volunteers are not
159 representative of the population as a whole (Davis, Coleman, et al., 2018; Fry et al., 2017), in
160 particularly under-representing people with lower socioeconomic status, people with chronic illness
161 and smokers. This means that the data cannot be used to estimate population prevalence.

162

163 The methods used to develop and implement the online MHQ, participation and features of non-
164 participants are described in Davis, Coleman, et al. (2018). All UKB participants with a valid email
165 address were sent a link in 2016-7 (n=339,092), and 46% of those invited submitted valid responses.
166 People who responded had an average age of 65 years and 57% were female. The questionnaire is
167 still open on the website for participants to complete. We report findings based on the dataset
168 released in August 2017 (n=157,363, 31% cohort).

169

170 The four main methods of classifying these participants' mental health are: symptom-based
171 outcomes, self-report of diagnosis, hospital data-linkage, and self-report of medication. Brief
172 explanations are provided below, with the full wording, criteria, cut-offs and code lists available in
173 the appendices of supplementary materials. Table 1 shows examples of each method for four
174 outcome groups that will be examined in results. Some of these groups will have more closely
175 aligned concepts that will allow comparison across methods, others will not. For example, psychotic
176 experiences (PE) are not a true 'symptom', and most people who have these experiences do not
177 have a psychotic disorder. Therefore self-report diagnosis and hospital data-linkage of psychotic
178 disorder should be viewed as complementary concepts to PE; whereas the depression outcome
179 group are more akin to different methods of ascertaining the same concept.

180

181 #Insert table 1 around here

182 Table 1: Summary of definitions for four measures (columns) that may be used to identify mental
183 health outcomes for four example outcome groups (rows)

184

185 Symptom-based outcomes

186 Lifetime depression, anxiety, bipolar affective disorder (BPAD) and psychotic experiences (PE) make
187 up the lifetime "symptom-based outcomes". Lifetime measures were felt to be important to

188 generate controls ("never had") for genetic studies. Depression was assessed using the major
189 depressive disorder section of the Composite International Diagnostic Interview Short Form (CIDI-
190 SF), and anxiety was assessed using the generalized anxiety disorder section of the CIDI-SF, modified
191 to provide lifetime history (Kessler, Andrews, Mroczek, Ustun, & Wittchen, 1998; Levinson et al.,
192 2017). There were chosen on the basis of the ability to map on to DSM criteria, results of the
193 validation study carried out by Levinson et al., and to maximise compatibility with studies
194 internationally that were looking at the genetics of depression and anxiety. The CIDI-SF uses DSM-IV
195 criteria, but is also likely to represent a DSM-5 diagnosis as criteria are largely unchanged (American
196 Psychiatric Association, 2013). Further questions assessed probable lifetime history of DSM-defined
197 hypomania/mania; criteria met for at least one week was used as the symptom-based outcome for
198 the BPAD outcome in this study. Lifetime PE, not in themselves a disorder, were assessed using
199 adapted questions from the CIDI (McGrath et al., 2015).

200

201 **Self-report of diagnosis**

202 Participants were asked about clinician diagnoses of any medical condition at the baseline UKB
203 interview, and were specifically asked about mental disorders in the MHQ. We only use the
204 prompted recall from the MHQ for this analysis. The questionnaire asked participants: "Have you
205 been diagnosed with one or more of the following mental health problems by a professional, even if
206 you don't have it currently?" Choices included "depression", "anxiety, nerves or generalised anxiety
207 disorder", "mania, hypomania, bipolar or manic-depression", "schizophrenia" and "other psychotic
208 illness".

209

210 **Hospital data linkage**

211 UKB has obtained structured diagnostic information from hospital admissions data to form a virtual
212 hospital registry, combining Hospital Episode Statistics (HES); Scottish Morbidity Record (SMR 1a and
213 1b); and Patient Episode Database for Wales (PEDW) into a single dataset (UK Biobank, 2014). Dates
214 and completeness of coverage vary: PEDW dates back to 1999, HES to 1997, and SMR to 1981. HES
215 and PEDW have mental health admissions in the same set as general hospital admissions, but
216 Scotland do not. At the time of extraction, the Scottish mental health admissions (SMR-04) were not
217 available in UKB. Therefore participants registered for the UKB in the two Scottish centres were
218 excluded from the comparisons that involve hospital data-linkage, leaving 146,813 participants in
219 England and Wales. HES and PEDW use World Health Organisation (WHO) International
220 Classification of Diseases 10th Revision (ICD-10) to categorise diagnosis (World Health Organization,
221 1992). Cases were defined as having ever received an ICD-10 diagnosis code relating to depression,

222 anxiety, BPAD or psychosis (see table 1 or appendix 3 in the supplementary material) in main or any
223 secondary diagnoses. Psychosis codes included depression and BPAD where psychotic symptoms
224 were specified.

225

226 **Self Report of Medication**

227 At baseline (2007-2010), six to ten years before completion of the MHQ, UKB participants were
228 asked whether they were taking any regular medication, and a nurse interviewer took the names of
229 medication taken. A pre-existing code list of antidepressants, antipsychotics and lithium
230 preparations was used to extract this data (see appendix 4 in supplementary material).

231

232 **Data and Analysis**

233 The study used the UKB data release application number 16577 (application by GB), including valid
234 MHQ data to June 2017 and hospital admission data 1997-2015, extracted and analysed using R
235 version 3.4.3 (R Core Team, 2017) and code written by JC and KD (Davis, Coleman, et al., 2018). Full
236 data is available from UKB (<http://www.ukbiobank.ac.uk/register-apply/>).

237

238 Confidence intervals are given at 95%, using Wilson's method for proportions. Cohen's kappa was
239 calculated as a measure of agreement between different methods of ascertainment for the same or
240 equivalent outcomes.

241

242 **Ethical approval**

243 UKB has ethical approval from the North West - Haydock Research Ethics Committee (11/NW/0382)
244 with MHQ approved as an amendment.

245 **Results**

246 **Self-reported Diagnosis**

247 Table 2 is a cross-tabulation of overlap between (i) self-reported lifetime diagnosis and (ii) symptom-
248 based outcomes. Percentages refer to the proportion of those with a self-reported diagnosis (row)
249 who met criteria for the specified symptom-based outcomes (column). Of those that reported any
250 mental disorder, 60% also met criteria for any symptom-based outcome, while only 15% of those
251 who reported no mental disorder met any criteria. The self-report status (any vs none) agreed with
252 the symptom-based status in 78%, with a kappa of 0.46. Nearly ninety percent of people reporting
253 BPAD or psychotic disorder met criteria for one or more symptom-based outcome. Regardless which
254 disorder was self-reported, lifetime depression was the most likely symptom-based outcome.

255

256 Depression, anxiety and BPAD self-reported diagnoses and symptom-based outcomes are compared
257 in table 3. Depression outcomes had a kappa of 0.46, anxiety outcomes have a kappa of 0.28 and
258 BPAD outcomes have a kappa of 0.24.

259

260 **Hospital data-linkage**

261 Table 4 shows the partial overlap between the symptom-based outcomes, self-reported diagnosis
262 and hospital data-linkage. The combination of three sources identified depression in 48,794
263 participants, but the hospital data-linkage only identified 3,034 (6%) of these, most of whom (1,937)
264 were also identified by both of the other two methods. Hospital data-linkage identified 5% of anxiety
265 cases and 9% of BPAD cases identified by any means. Of those with hospital data-linkage diagnosis of
266 psychotic illness (213), the symptom-based outcome of PE was present in 67% (143).

267

268 **Self-Reported Medication**

269 The snapshot view of selected self-report medication use provided at the baseline assessment is
270 shown in tables 5a-c. Antidepressants were being taken by 8,616 (5.9%) participants, while
271 antipsychotics and lithium were prescribed to less than 500 people each. Eighty-three percent (83%)
272 of all people taking antidepressants were identified as having a lifetime history of depression
273 through one of the three methods. Only half of the participants taking antipsychotics reported PEs
274 or had a diagnosis of psychosis (229/470, 49%), although a further 35% (163/470) had an indicator of
275 affective disorder. Lithium was almost confined to those identified as having an affective disorder –
276 79% BPAD, 20% depression without evidence of BPAD.

277

278 **Combinations**

279 Table 4 shows the results of combining symptom-based outcomes, self-reported diagnosis and
280 hospital data-linkage in an additive manner for depression, anxiety and BPAD. In all disorders,
281 symptom-based outcomes, self-report and hospital data-linkage each contribute unique cases – but
282 in different proportions for each disorder.

283

284 Combinations of outcomes for the common mental disorders of depression and anxiety are further
285 explored in table SM1 and accompanying text. The symptom-based outcomes were positive for
286 depression or anxiety in 37,629 participants. Self-reported or data-linkage diagnosis of depression or
287 anxiety or self-reported antidepressant medication is positive in 47,321 participants, including
288 25,920 (55%) who were positive and 21,401 (45%) who were negative on lifetime symptom-based
289 outcomes.

290

291 Discussion

292 In this study we have compared methods of ascertainment for mental health outcomes in UKB from
293 the position that none is equivalent to the outcome of a gold-standard psychiatric interview. This
294 situation is common in large non-specialist research resources, and there is a need for resources to
295 help with decision-making when researchers are faced with a choice of imperfect measures.

296

297 We found that the magnitude of the overlap between the measures differed depending on the
298 disorders. Depression outcomes were the most prevalent and had the most overlap between self-
299 report and symptom-based outcomes ($\kappa=0.46$). The proportion of participants with symptom-
300 based outcome who self-reported a diagnosis was 55%, similar to the 61% of people of a similar age
301 in a German study who were positive for lifetime depression on the SCID-I who self-reported a
302 diagnosis (Stuart et al., 2014).

303

304 A self-reported diagnosis of "anxiety, nerves or generalised anxiety disorder" had less overlap with
305 the corresponding symptom-based outcome ($\kappa=0.28$), a symptom-based outcome for
306 depression (53%) being more likely than anxiety (26%). Combining depression and generalised
307 anxiety may be an acceptable strategy in population studies, where the concepts are largely
308 overlapping (Gask, Klinkman, Fortes, & Dowrick, 2008), and in our data this led to an improvement in
309 agreement between self-report and symptom-based outcomes over anxiety, but not depression
310 ($\kappa=0.46$).

311

312 The conventional models of BPAD, with dramatic and disabling symptoms, would predict a high
313 proportion to have been formally identified, but our symptom-based outcome of BPAD was
314 deliberately fairly wide to facilitate research into the wider spectrum of BPAD (Phillips & Kupfer,
315 2013), and would include many people who would meet the DSM criteria for BPAD type II as well as
316 BPAD type I. People with BPAD type II will be less likely to be formally diagnosed or require inpatient
317 treatment, and hence will be less commonly identified by a hospital data-linkage. Of those with
318 BPAD symptom-based outcome, 16% self-reported clinician diagnosis and 9% had data-linkage
319 diagnosis. Self-report diagnosis is somewhat higher in this study than in a similar Finnish population
320 study (Perälä et al., 2007) where only 6% of those positive for the CIDI-BPAD outcome self-reported
321 a diagnosis. This may be evidence of a cohort effect of different diagnostic behaviour or patient
322 awareness between countries or over time.

323

324 PE and psychotic disorder are not equivalent, but complementary categories. We found that PE was
325 almost ten times more common than psychotic disorder reported by the participant and/or hospital
326 data-linkage (prevalence of PE 4.7% vs psychotic disorder diagnosis 0.5%). The Finnish study (Perälä
327 et al., 2007) found the rates of PE and psychosis diagnosis to be 3.0% and 3.3% respectively. The
328 lower prevalence of PE may be partly due to the mode of administration being interview, as PE are
329 more likely to be endorsed in self-completed measures (Linscott & Van Os, 2013). The higher levels
330 of diagnosis of a psychosis diagnosis may be partly because the registry used in the Finnish study
331 goes back further in time, but may also be related to participation bias. The Finnish study was a
332 modest size study aiming at representativeness, with a participation rate of 93% of those selected,
333 whereas UKB followed a different model, requesting volunteers from the community (Davis,
334 Coleman, et al., 2018; Fry et al., 2017): people with an enduring psychotic disorder may have been
335 less willing and/or able to volunteer.

336

337 Of the three self-reported medication classes investigated, antidepressants were the most
338 commonly reported. Even so, antidepressant prescription could only identify 15-17% of people with
339 those symptom-based outcomes of depression and anxiety. This is inevitable given the snapshot
340 nature of the ascertainment of medication, the "treatment gap" (Kohn, Saxena, Levav, & Saraceno,
341 2004), and appropriate management of lifetime mental disorder without medication. Surprisingly,
342 only 49% of those taking antipsychotics were positive on a measure of PE or psychosis, 35% had an
343 affective disorder and 13% neither. This fits with literature on the extended and off-label prescribing
344 of antipsychotics (Carton et al., 2015; Pringsheim, Gardner, & Patten, 2015).

345

346 **Method of ascertainment**

347 Symptom-based outcomes do not require participants to have accessed care to detect a disorder,
348 making them potentially the most sensitive out of the measures we compared, although the
349 retrospective nature is likely to reduce sensitivity for distant episodes. By analysing participant
350 responses to particular questions, it may also be possible to also look at subtypes or specific
351 phenotypes or manipulate thresholds. Symptoms were collected using CIDI-SF modules. The CIDI
352 was created for the World Health Organisation (WHO) programme, and supported by them,
353 although the short form is not currently supported by the WHO. Such measures are popular in
354 surveys (McDowell, 2006; van Ballegooijen, Riper, Cuijpers, van Oppen, & Smit, 2016), although they
355 can be over-inclusive as they lack the ability to rule out other causes of the same symptoms (e.g.
356 thyroid disturbance mimicking anxiety). Alternatives to the CIDI-SF may have different, possibly
357 better, performance – but this has not been tested.

358

359 Administration of self-report diagnostic scales online is now an established practice (Andersson et
360 al., 2008; Nguyen, Klein, Meyer, Austin, & Abbott, 2015), but there is generally less validation data
361 available for measures administered electronically or via the internet (Buchanan, 2003; van
362 Ballegooijen et al., 2016). The performance of the CIDI-SF modules that were administered in the
363 online MHQ have been positively validated in at least two independent studies (Carlbring et al.,
364 2002; Levinson et al., 2017).

365

366 Self-reported clinician diagnosis is an easily obtainable measure, which allowed the MHQ to ask
367 about a wide range of outcomes. As predicted, the diagnosis prevalence was lower than the
368 symptom-based outcome prevalence in the MHQ in most categories. The exception was generalised
369 anxiety – which may be related to the wording of the question regarding anxiety diagnosis being
370 vague. The presence of self-reported diagnosis was associated with a greater risk of all symptom-
371 based outcomes, not just for equivalent outcomes, which reflects the comorbidities between
372 disorders often unrecognised (Oiesvold et al., 2013; Whiteford et al., 2015). Another source of self-
373 reported diagnosis in UKB are those reported during the baseline assessment. On that occasion,
374 participants were not prompted to recall specific diagnoses, and had to disclose them face-to-face.
375 The prevalence of self-reported mental prevalence was lower on that occasion, with depression
376 reported by only 6.5%, as opposed to 21% at the MHQ. This is likely to do with the prompted recall,
377 but may also be due to stigma during a face to face interview and new diagnoses since baseline.

378

379 The hospital data-linkage provided by UKB leverages national statistics to identify outcomes that are
380 commonly documented in hospital admissions. The nature and patient pathway of mental disorders
381 mean only the most severe cases are likely to be the cause of an admission (Goldberg & Huxley,
382 1980). Moreover, these episodes may have happened many decades ago, before 1997 when the
383 data for England starts. Most mentions of mental disorder will therefore be secondary diagnoses in
384 participants admitted to hospital with other problems, which have not been specifically validated
385 (Davis, Bashford, et al., 2018). In this study, the low numbers identified in hospital data-linkage, with
386 high levels of lifetime symptom-based outcomes in those individuals, suggests a specific but
387 insensitive measure. Registries based on data-linkage to outpatient attendance or primary care
388 consultations may give a more sensitive measure, although it is likely to be more complex to define
389 cases given the myriad of coding types in these records (John et al., 2016; Spiranovic, Matthews,
390 Scanlan, & Kirkby, 2016).

391

392 The use of self-reported medication data is potentially problematic. Bias in recall of medication is
393 very common, perhaps more so in psychotropics (Gnjidic, Du, Pearson, Hilmer, & Banks, 2017).
394 Objective ascertainment of prescribed medication is likely to be provided in the future by linkage to
395 primary care data, and in some studies, pharmacy claims data has been successfully used to
396 supplement self-reported medication (Drieling et al., 2016; Gnjidic et al., 2017). However, there will
397 remain the likelihood that medication will have poor sensitivity for case finding in mental health, as
398 psychotropics will never be prescribed to all of those with a lifetime history, and poor specificity as
399 they are prescribed for many things outside of mental health. In the case of using medication in the
400 UKB to supplement MHQ findings, there is the added problem of the snapshot of medication taken
401 being ascertained around seven years prior to the MHQ administration, and therefore being unable
402 to reflect new-onset disorders and prescriptions.

403

404 Algorithmic approaches can be taken that exploit the strengths of each measure to produce a
405 compound measure. Algorithms will include combining cases from two or more outcome types as
406 done for this genomic study of depression in UKB using baseline self-report and hospital diagnosis
407 (Howard et al., 2018). Items can also be grouped into new criteria as was done to define mood
408 disorders at baseline (Smith et al., 2013). Another approach, previously suggested in the case-control
409 definitions defined by the UKB mental health outcomes group, uses symptom-based outcomes for
410 cases, but exclude from controls those who self-reported diagnosis or had data-linkage diagnosis or
411 suggestive medication. Taking the BPAD row from table 4 as a simplified example: 2,247 people
412 were positive for the symptom-based outcome and 155,119 were negative; out of those who did not
413 meet criteria, 177 had a hospital diagnosis of BPAD, 326 more reported a diagnosis of BPAD; and 35
414 more reported taking lithium (table 5c)– all of these are suggestive of BPAD. To minimise false-
415 positives and false-negatives in the BPAD item, these 538 suggestive participants can be excluded
416 from cases and controls, leaving 2,247 cases and 154,581 controls. Further algorithms incorporating
417 hospital and primary care data for severe mental illness and common mental disorder in the full
418 cohort are due to be published by UKB in 2019-20 – as has already been done for stroke and
419 myocardial infarction.

420

421 **Does it matter?**

422 We have shown that different methods of ascertainment of mental disorder can result in different
423 groups of participants being identified as cases. This poor agreement between methods of
424 ascertainment could be problematic for research consistency and reproducibility. However, there is
425 evidence that even with poor agreement at the level of disorder diagnosis, there can be similarity at

426 the biological level. For example, a twin study (Torvik et al., 2018) reported that cases derived from
427 interview diagnoses had limited overlap with those selected by data-linkage (primary and secondary)
428 – for depression 36% interview positive were also on primary care registry, while 48% of those in
429 registry were interview positive, with less overlap for anxiety (21%/46%) and alcohol use disorder
430 (3%/33%). Despite this, the genetic features identified in the interview and registry groups were
431 highly correlated within each diagnosis, approaching unity for depression and anxiety disorders. It
432 remains to be seen whether the same will be true for the different cohorts selected in UKB –
433 certainly focussing exclusively on very highly selected outcomes such as hospital data-linkage means
434 including biases to do with health service utilisation that may not relate to underlying mental health
435 need (Roberts et al., 2018).

436

437 Genome-wide association studies (GWAS) often pool cases and controls from different cohorts.
438 Studies that define DSM disorders using clinical interview, self-report diagnosis, symptom-based
439 outcomes, or combinations thereof might be combined in order to achieve the necessary size of
440 sample. The results will then depend heavily on whether the biology converges on a single disorder
441 or converges on the different definitions (Vrieze, Iacono, & McGue, 2012). A massed GWAS of
442 depression (Wray et al., 2018) included cases that were defined at interview (PGC29, GenScot),
443 treatment registers (iPSYCHE, GERA), self-report diagnosis (23andMe) and a combination (DeCODE,
444 UKB [prior to MHQ results]) showed strong genetic correlation between the studies. The combined
445 GWAS also showed enrichment of the targets of antidepressant treatment. These results suggest
446 that weakening the phenotype can reveal interesting and relevant biology.

447

448 On some occasions, we have found that different measures have indicated different disorders for
449 the same individuals, which could lead to confusion in research concentrated on a narrowly defined
450 diagnosis. However, this reflects established findings of a high degree of comorbidity and cross-over
451 in mental disorders (Davis, Bashford, et al., 2018; First, 2005; Gask et al., 2008), probably due to
452 shared etiology and pathology (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013;
453 Elliott, Romer, Knodt, & Hariri, 2018) that is poorly translated into categorical diagnostic
454 classifications. Other models for understanding mental disorder have been suggested, and some of
455 these ideas could be translated to measures for research in large cohorts (Carcone & Ruocco, 2017;
456 Clark et al., 2017; Vrieze et al., 2012), but diagnostic categories continue to be utilised widely.

457

458 **Implications**

459 For users of UKB, the symptom-based outcomes defined in the MHQ offers advantages: they will
460 select a large proportion of the participants with a likely disorder; many have been validated
461 externally; and there is scope to customise, such as for different thresholds. However, self-report,
462 hospital data-linkage and medication may also be able to identify unique cases, and may have high
463 predictive validity. In some cases, it would seem sensible to add cases together. Another approach is
464 to use the symptom-based outcome to define the cases, and define the controls to exclude positives
465 on the other measures. For some questions, the sample and measures in the MHQ may be too
466 limiting, and unprompted baseline self-report supplemented by hospital data-linkage will have to be
467 used (Howard et al., 2018), which are highly selected, until primary care data and algorithms are
468 released. Comorbidity between mental disorders is high, and interpretation of this may need
469 consideration. Given the high degree of flexibility that UKB affords, researchers should consider the
470 breadth and granularity of the mental health diagnosis needed alongside the consideration of the
471 variables used to define them, so that the most appropriate combination of measure and outcome
472 can be chosen to best address the research question.

473

474 Other studies could learn from the experience in UKB in three main ways. Firstly, under-recognition,
475 fluctuating course and self-management of most mental disorder means questions about lifetime
476 symptoms are needed to identify those who have never had a disorder. Second, comorbidity
477 between the mental disorders is high, and this needs to be acknowledged in the design and
478 interpretation of mental health questionnaires. Thirdly, registries, data-linkage and measures of
479 treatment will underestimate numbers of cases of mental disorder, but do provide further
480 information.

481

482 **Strengths and weaknesses**

483 UKB aims to produce and adjudicate outcomes in a clear, expert-led manner. The Mental Health
484 Outcomes Consortium has worked with UKB to implement the MHQ, and the present analysis was
485 planned to clarify the different mental health definitions now present in UKB.

486

487 The MHQ had a very good response rate compared with previous UKB online questionnaires, and it
488 gives an unparalleled sample size for a mental health survey. However, like much observational
489 research, it is subject to participation bias in its volunteers (Davis, Coleman, et al., 2018; Fry et al.,
490 2017). Given that participation in research can be patterned by mental health (Atherton, Fuller,
491 Shepherd, Strachan, & Power, 2008; Knudsen, Hotopf, Skogen, Øverland, & Mykletun, 2010), it may
492 be that people with severe symptoms of mental disorder were less likely to volunteer or complete

493 the MHQ, as might be suggested by the small number of people with a hospital data-linkage
494 diagnosis of a psychotic disorder, which may limit generalisability of our findings to other settings.
495

496 The measures in the MHQ were felt to be the most suitable for defining lifetime mental disorders
497 within the constraints of a short survey and maintaining compatibility with existing genetic studies.
498 The online CIDI-SF has been validated, but only for depression in the lifetime version. The questions
499 used to assess for symptoms of mania / hypomania have not been externally validated. For both
500 instruments, it is likely that the lifetime version is affected by recall bias. Further, the UKB data-
501 linkage and medication aspects are currently limited. Hospital admission data will capture few with
502 mental disorders, so we will welcome the forthcoming linkages to primary care data. Medication was
503 self-reported and on a single occasion that was seven to ten years prior to the symptom-based
504 outcome: again it may be better after linkage to primary care data.

505

506 **Conclusions.**

507 Large cohort studies provide great potential for interesting discovery, but using these datasets
508 involves confronting problems with definitions of disorders, data quality and incomplete coverage.
509 Mental health research is further hampered the challenge that many mental disorders are under-
510 recognised and under-represented in healthcare data. UKB is a rich observational resource due to its
511 size, extensive baseline measures and linkages to national administrative records. The utility of UKB
512 for mental health research has been improved by the UKB MHQ. We have shown that, in general,
513 the numbers of cases identified by lifetime symptom-based diagnosis exceeds those identified with
514 self-report diagnosis, hospital data-linkage and psychotropic medication, with an overlap between
515 measures that differs between the disorders under study. The advantage of symptom-based lifetime
516 classification of mental disorder is sensitivity across the severity spectrum, and many of the
517 symptom-based outcomes have been validated against psychiatric interview elsewhere. However,
518 other mental health ascertainment methods could complement symptom-based outcome measures
519 in research. UKB and other open science projects lend themselves to innovative, well-described and
520 reported approaches that can be scrutinised by the community. The ideas and results of this
521 exploratory analysis highlight the strengths and limitations of both the indicators in large cohort
522 studies, and the mental disorder diagnosis itself, which we hope will assist those planning to address
523 the important questions in mental health and wider research.

524

ix)

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Table 1: Summary of definitions for four measures (columns) that may be used to identify mental health outcomes for five example outcome groups (rows)

	Symptom-based outcome (see also appendix 2)	Self-report diagnosis	Hospital data-linkage 1997-2015 (see also appendix 3)	Self-report medication 2007-10 (see also appendix 4)
Depression outcomes	Positive for major depressive disorder ever in MHQ (CIDI-SF lifetime). Prevalence 24%	Endorsed clinician diagnosis of "depression" in MHQ. Prevalence 21%	Diagnosis of ICD-10 depressive disorder (F32-33) on inpatient record. Prevalence 2%	Reported use of an antidepressant (prevalence 5%), antipsychotic (prevalence 0.3%) or lithium (prevalence 0.1%) at baseline.
Anxiety outcomes	Positive for generalised anxiety disorder ever in MHQ (CIDI-SF lifetime). Prevalence 7%	Endorsed clinician diagnosis of "anxiety, nerves or generalised anxiety disorder" in MHQ. Prevalence 14%	Diagnosis of ICD-10 neurotic disorders (F4x) on inpatient record. Prevalence 1%	Reported use of an antidepressant at baseline. Prevalence 5%
Bipolar affective disorder (BPAD) outcomes	Positive for wider bipolar criteria ever in MHQ (reflecting DSM IV hypomania/mania criteria). Prevalence 2%	Endorsed clinician diagnosis of "mania, hypomania, bipolar or manic-depression" in MHQ. Prevalence 1%	Diagnosis of ICD-10 mania or BPAD (F30-31) on inpatient record. Prevalence 0.2%	Reported use of lithium (prevalence 0.1%) or an antipsychotic (prevalence 0.3%) at baseline.
Psychotic experience (PE) outcomes	Endorsed one or more of four PEs ever (adapted CIDI PE lifetime)*. Prevalence 5%	Endorsed clinician diagnosis of "schizophrenia" or "other psychotic illness" in MHQ. Prevalence 1%	Diagnosis of ICD-10 schizophrenia spectrum (F2x) or affective psychosis (F30.2, F31.2, F31.5, F32.3, F33.3) on inpatient record. Prevalence 0.1%	Reported use of antipsychotic at baseline. Prevalence 0.3%

Footnotes

*PE are not true 'symptoms' but outcome that can be related to psychotic disorder

BPAD: Bipolar affective disorder; CIDI-SF: Composite International Diagnostic Interview Short Form; ICD-10: International classification of diseases; PE: Psychotic experience

Prevalence refers to criteria positive in this sample of 157,363 UKB volunteers who completed the MHQ.

Tables 2: Symptom-based outcomes (SBO, columns) and self-reported diagnoses (SR, rows). Numbers define participants with both stated symptom-based outcome and self-report (SBO \cap SR) and % is proportion of participants with given self-report also having given symptom-based outcome (SBO | SR).

		Overall		Symptom-based outcome (SBO)					
		n.	prev. in sample	n. SBO \cap SR (SBO SR %)					
				Depression	Anxiety	Wide bipolar definition	PE*	Any SBO	No SBO
Overall	n.	157363	na	37434	11111	2396	7803	44598	112765
	prev. in sample	na	na	24%	7%	2%	5%	28%	72%
Self-report diagnosis (SR)	Depression	33424	21%	20714 (62%)	7173 (21%)	1314 (4%)	3239 (10%)	22651 (68%)	10773 (32%)
	Anxiety	22036	14%	11632 (53%)	5711 (26%)	813 (4%)	2051 (9%)	13365 (61%)	8670 (39%)
	BPAD	837	1%	599 (72%)	248 (30%)	391 (47%)	358 (43%)	737 (88%)	100 (12%)
	Psychosis	723	1%	491 (68%)	247 (34%)	187 (26%)	458 (63%)	635 (88%)	88 (12%)
	Panic disorder	8704	6%	4555 (52%)	2424 (28%)	399 (5%)	1024 (12%)	5273 (61%)	3431 (39%)
	Eating disorder	1851	1%	1048 (57%)	495 (27%)	101 (5%)	279 (15%)	1201 (65%)	650 (35%)
	Personality disorder	385	<1%	270 (70%)	171 (44%)	63 (16%)	141 (37%)	324 (84%)	61 (16%)
	Any self-report	48230	31%	25495 (53%)	9081 (19%)	1721 (4%)	4255 (9%)	28739 (60%)	19491 (40%)
	No self-report	109133	69%	11938 (11%)	2030 (2%)	675 (1%)	3548 (3%)	15859 (15%)	93274 (85%)

Footnotes: BPAD = bipolar affective disorder, PE = psychotic experience

*PE are not true 'symptoms' but outcome that can be related to psychotic disorder

For definitions of symptom-based-outcomes, please see appendix 2 in supplementary material.

Table 3: The overlap of self-report (A) and symptom-based outcome (B) for selected diagnoses, showing the intersect ($A \cap B$), proportion overlap ($B|A$ & $A|B$) and agreement (kappa).

	n. Self-report (A)	n. Symptom-based outcome (B)	n. Self-report AND Symptom-based outcome ($A \cap B$)	% Symptom-based outcome given Self-report ($B A$)	% Self-report given Symptom-based outcome ($A B$)	kappa
Depression	33424	37434	20714	62%	55%	0.46
Anxiety	22036	11111	5711	26%	51%	0.28
BPAD	837	2396	391	47%	16%	0.24

Footnotes: BPAD = bipolar affective disorder

Table 4: Identification of five mental health outcomes using symptom-based outcomes, self-report diagnosis and hospital data-linkage, for participants from England and Wales (n=146,813).

	Any	Symptom criteria (a)		Self-report (b)		Hospital data-linkage (c)		Combinations			
		Total	Alone	Total	Alone	Total	Alone	a∩b	a∩c	b∩c	all three
Depression	48794	35140 (72%)	15472 (32%)	31381 (64%)	11919 (24%)	3034 (6%)	257 (1%)	19462 (40%)	2143 (4%)	2571 (5%)	1937 (4%)
Anxiety	35136	16806 (48%)	8324 (24%)	26124 (74%)	17264 (49%)	1770 (5%)	555 (2%)	8349 (24%)	704 (2%)	571 (2%)	571 (2%)
BPAD	2709	2247 (83%)	1875 (69%)	783 (29%)	337 (12%)	245 (9%)	37 (1%)	364 (13%)	194 (7%)	120 (4%)	112 (4%)
PE*	7686	7390 (96%)	6920 (90%)	684 (9%)	226 (3%)	213 (3%)	46 (1%)	434 (6%)	143 (2%)	131 (2%)	107 (1%)

Footnotes: See table 1 and appendices for definitions. BPAD = bipolar affective disorder, PE = psychotic experience

*PE are not true 'symptoms' but outcome that can be related to psychotic disorder. Self-report and hospital data-linkage, in contrast, represent psychotic disorders.

Total = n. participants positive on given measure for given outcome (% positive for measure / positive for outcome).

Alone = n. participants that were positive for given measure and not for other measures in given outcome (% positive for this measure alone / positive for outcome)

Combinations: x∩y = participants positive for both given criteria, irrespective of whether positive for third

Table 5a-c: Self-reported psychotropic use at baseline against psychiatric indication by three criteria: symptom-based outcome, self-report diagnosis and hospital data-linkage. % = proportion of cases screening positive for each criteria who reported medication use, except bottom row. Bottom row shows proportion of all participants reporting medication use who screened positive for each disorder.

(a) Self-report of any antidepressant for participants with depression and anxiety outcomes.

	Depression	Anxiety	Nil
Symptom-based outcome	5352/35140 (15.2%)	2355/10415 (22.6%)	
Self report diagnosis	6378/31381 (20.3%)	4427/26124 (16.9%)	
Hospital data-linkage	1492/2858 (52.2%)	533/1770 (30.1%)	
Self-report antidepressant given above criteria	7137/47278 (15.1%)	5123/31071 (16.5%) <i>excluding depression</i> 556/10829 (5.1%)	923/88706 (1.0%)
Any criteria given self-report antidepressant	7137/8616 (82.8%)	<i>excluding depression</i> 556/8616 (6.5%)	923/8616 (10.7%)

Footnotes: See table 1 and appendices for definitions.

(b) Self-report of any antipsychotic for participants with psychotic experiences or psychotic disorder (PE), BPAD and depression outcomes.

	PE*	BPAD	Depression	Nil
Symptom-based outcome	203/7390 (2.7%)	103/2247 (4.6%)	300/35140 (0.9%)	
Self report	163/684 (23.8%)	135/783 (17.2%)	277/31381 (0.9%)	
Hospital data-linkage	84/213 (39.4%)	68/245 (27.8%)	105/2858 (3.7%)	
Self-report antipsychotic given above criteria	229/7686 (3.1%)	161/2709 (5.9%) <i>excluding PE</i> 42/1890 (2.2%)	354/47278 (0.7%) <i>excluding PE and BPAD</i> 121/41359 (0.3%)	78/95879 (0.1%)
Any criteria given self-report antipsychotic	229/470 (48.7%)	<i>excluding PE</i> 42/470 (8.9%)	<i>excluding PE and BPAD</i> 121/470 (25.7%)	78/470 (16.6%)

Footnotes: See table 1 and appendices for definitions. BPAD = bipolar affective disorder, PE = psychotic experience

*PE are not true 'symptoms' but outcome that can be related to psychotic disorder. Self-report and hospital data-linkage, in contrast, represent psychotic disorders.

(c) Self-report of lithium prescription for participants with BPAD and depression outcomes.

	BPAD	Depression	Nil
Symptom-based outcome	73/2247 (3.2%)	127/35140 (0.4%)	na
Self report	119/783 (15.2%)	111/31381 (0.4%)	na
Hospital data-linkage	67/245 (27.3%)	50/2858 (1.7%)	na
Self-report lithium given above criteria	131/2709 (4.8%)	146/47278 (0.3%) <i>excluding BPAD</i> 34/45195 (0.1%)	1/98909 (0.0%)
Any criteria given self-report lithium	131/166 (78.9%)	<i>excluding BPAD</i> 34/166 (20.5%)	1/166 (0.6%)

Footnotes: See table 1 and appendices for definitions. BPAD = bipolar affective disorder

xi) Figure headers

Nil

xii) Appendices

Table SM1: Overlap of routine items for common mental disorder and symptom-based outcome for common mental disorder

Appendix 1: Questionnaire wording and format

Appendix 2: Case Criteria Derived from the UK Biobank Mental Health Questionnaire

Appendix 3: ICD-10 codes used for hospital data-linkage

Appendix 4: UKB medication codes used