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# UK Biobank prospective cohort design and analytical considerations

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53 **Overline: Biobanks**

54

55 **One sentence summary:** This article describes approaches to study design, resource  
56 access and data analysis in UK Biobank to facilitate health-related research

57

58 **Abstract**

59 Population-based prospective studies are valuable for generating and testing hypotheses  
60 about the potential causes of disease. We describe how the approach to UK Biobank's study  
61 design, data access policy, and statistical analysis can minimise error and improve the  
62 interpretability of research findings, with implications for other studies being established  
63 worldwide.

64

## 65 Introduction

66 Population health research has come a long way in the last few decades, with major advances  
67 in our understanding of the causes of disease. In particular, prospective studies that were  
68 initiated in the 1950s, such as the British Doctors Study (1) and the Framingham Heart Study  
69 (2), have been invaluable for understanding the association between lifestyle factors and  
70 disease risk as they overcome many of the biases inherent in case-control studies (most  
71 notably that exposures (i.e. risk factors for disease) are measured prior to disease onset).  
72 However, until recently, the conclusions that could be drawn from such studies were limited  
73 by small sample size, varying analytical approaches taken to define various risk factors and  
74 the relatively short duration of follow-up time to assess health outcomes. It was not until data  
75 from these different studies were integrated into large-scale individual-level meta-analyses  
76 that associations of exposures with disease risk were identified robustly. For example, it is  
77 now well established that circulating lipids and blood pressure are causally related to vascular  
78 disease (3), adiposity with cardiovascular disease (4), menopausal hormone therapy use and  
79 alcohol consumption with breast cancer (5, 6) and oral contraceptive use with a reduced risk  
80 of ovarian cancer (7).

81 More recently, there has been remarkable progress in research on the genetic  
82 determinants of disease. In the early 2000s, the literature was dominated by a plethora of  
83 genetic studies that focused on associations with particular conditions within specific  
84 “candidate” genes that were of *a priori* interest. Many of these studies involved small numbers  
85 of disease cases and yielded false-positive results that failed to replicate, often because of  
86 undue emphasis on *post hoc* selective reporting of the more extreme associations that were  
87 observed. Subsequently, improvements in assay technology led to genome-wide association  
88 studies (GWAS) that allowed hypothesis-free identification across the genome of variants  
89 associated with a particular phenotype. Much effort was typically spent on characterising the  
90 phenotype under investigation precisely in the belief that outcome misclassification would

91 have a substantial impact on the ability to detect associations. However, when meta-analyses  
92 of different studies were performed that yielded much larger numbers of individuals with the  
93 outcome of interest (albeit differently defined), small-to-moderate associations between  
94 genetic variants and outcomes began to be identified reproducibly after stringent adjustment  
95 for multiple testing (8).

96 Even larger sample sizes – of the order of hundreds of thousands of participants – are  
97 needed to study gene-environment interactions, especially where the genetic variant or  
98 environmental exposure of interest is rare or has a small effect on disease risk (9).  
99 Consequently, there is a strategic need to establish large-scale, well-characterised,  
100 population-based prospective cohorts in which biological samples are collected and health  
101 outcomes are followed long-term to facilitate research into the determinants of disease.

#### 102 **UK Biobank combines scale, depth, duration and accessibility**

103 UK Biobank is a population-based prospective cohort of 500,000 men and women designed  
104 to enable research into the genetic, lifestyle and environmental determinants of a wide range  
105 of diseases of middle-to-old age ([www.ukbiobank.ac.uk](http://www.ukbiobank.ac.uk)). It was established by the UK Medical  
106 Research Council (MRC) and Wellcome, which continue to fund it along with the British Heart  
107 Foundation (BHF), Cancer Research UK (CR-UK) and National Institute for Health and Care  
108 Research (NIHR). The key design features are its easy accessibility, large-scale prospective  
109 nature, depth and range of risk factor data, and comprehensive linkage to health outcomes,  
110 which together enable academic and industry researchers worldwide to perform discovery  
111 science (Supplementary Table 1).

112 UK Biobank was designed to promote innovative science by maximising access to the  
113 data in an equitable and transparent manner. All approved researchers (academic or  
114 commercial) can access all of the de-identified data in order to perform any type of health-  
115 related research that is in the public interest. This is the key criterion against which applications

116 to access the data are considered, with restrictions only placed on their use for potentially  
117 contentious research (for example, investigations that could lead to racial or sexual  
118 discrimination). Access to biological samples is currently largely restricted to assays that will  
119 be conducted on the whole cohort or large representative samples of the cohort.

120           Ready access to such a large-scale, in-depth resource has encouraged researchers  
121 from many disciplines across academia and industry to collaborate to ensure that different  
122 types of complex data (e.g., whole-exome and whole-genome sequencing data, magnetic  
123 resonance imaging (MRI) scans, accelerometer wave-form data, and electronic health  
124 records) are generated and analysed appropriately. The ready accessibility of the data at low  
125 cost without requiring collaboration with, or peer review from, the UK Biobank study  
126 investigators has led to an exponential increase in research output. By the end of 2023, there  
127 were more than 30,000 registered researchers (80% from outside the UK) and about 9,000  
128 publications (attracting 270,000 citations), with the number of publications increasing  
129 exponentially each year. In particular, the release to the worldwide research community of  
130 cohort-wide genome-wide genotyping and imputation data in 2017 has been hugely influential  
131 in advancing our understanding of the genetic determinants of disease.

132           The requirement that researchers publish their findings and make available any  
133 derived variables that have been generated as part of their research, together with the  
134 underlying code that generated the research output, enables the wider scientific community to  
135 critique, modify and build upon the work of others in a transparent manner (10). For example,  
136 research groups with expertise in signal processing have created derived variables related to  
137 the intensity and duration of physical activity from the raw accelerometer data (11, 12).  
138 Similarly, academic and commercial research groups with expertise in image analysis have  
139 made available variables derived from the MRI scans related to body fat distribution (13), fat  
140 and iron content of specific organs (14, 15) and metrics of the structure and function of the  
141 brain (16) and heart (17). In this way, complex data that might otherwise only be of use to

142 specialists in a narrow field of research are turned into well-curated derived variables that are  
143 integrated with other UK Biobank data and can be used extensively by non-specialists to  
144 answer a range of research questions.

145 Easy access to such a wealth of data has led to new ways of presenting results. For example,  
146 summary statistics of all of the associations of individual genetic variants (18, 19) and  
147 polygenic risk scores (20) with a wide range of phenotypes are now available via online  
148 browsers. This move towards the publication of all summary results rather than publication of  
149 particular results in traditional scientific journals (where cherry-picking the most 'interesting'  
150 associations may introduce bias) is likely to accelerate scientific discovery and provide easier  
151 replication of associations across different studies. To help democratise access further, UK  
152 Biobank launched a cloud-based Research Analysis Platform in 2021 that allows streamlined  
153 access for researchers worldwide (in particular to the genome sequence data that are too  
154 large to transfer to researchers), as well as free computing and data storage for researchers  
155 from low- and middle-income countries and for early career researchers.

156 One consequence of researchers with different expertise accessing this wealth of data is the  
157 potential for unfamiliarity with various types of biases that are inherent in prospective studies  
158 that might influence results, as well as with the complexities associated with data that are  
159 outside of their areas of expertise. All researchers accessing biomedical resources to study  
160 the determinants of disease need to be aware of small sample size (that may produce  
161 imprecise estimates due to random error), incomplete or inadequate measurement of risk  
162 factors (that may lead to systematic under-estimation of disease associations), and health  
163 outcomes (that may lead to more imprecise estimates) and their potential confounding factors  
164 (that may obscure or lead to spurious associations between exposures and outcomes).  
165 Insufficient duration of follow-up may also lead to reverse causation bias, whereby the disease  
166 process influences potential risk factors (in particular, non-genetic ones), especially for  
167 conditions with a long prodromal phase, such as Alzheimer's disease.



168 UK Biobank has been set up to help minimise random and systematic error so that it  
169 can support reliable research into the determinants of disease (Supplementary Table 1),  
170 although the general principles of careful study design and appropriate data analysis apply  
171 equally to all large-scale, prospective studies. There are a number of trade-offs that need to  
172 be considered when designing a cohort study, which relate to the size and heterogeneity of  
173 the study population, and to the methods used for its recruitment, data collection and follow-  
174 up. UK Biobank has aimed to generate a large-scale, prospective biomedical resource that  
175 includes a wide range of exposure and health outcome measures collected as accurately as  
176 possible, with easy accessibility to the data. However, as with all prospective studies, it is  
177 important to consider, and if possible correct for, potential biases arising from the study design  
178 and collection of data.

### 179 **The importance of a large-scale prospective design**

180 UK Biobank recruited 502,000 volunteers aged 40-69 years at recruitment between  
181 2006 and 2010 from across England, Wales and Scotland. This age group was selected to  
182 include individuals who were young enough that relatively few would have developed health  
183 conditions at the time of recruitment. As a prospective study, UK Biobank has many  
184 advantages for investigating the effects of genetic, lifestyle and environmental factors on  
185 disease outcomes (21). In particular, information on exposures to potential risk factors can be  
186 assessed before disease develops, which avoids bias caused by differential recall of  
187 information about past exposures depending on an individual's outcome status (recall bias).  
188 The prospective design also allows investigation of factors that might be affected by disease  
189 processes or their treatment, or by changes in an individual's behavior following the  
190 development of some condition (reverse causation bias). In addition, it can support studies of  
191 conditions that cannot readily be investigated retrospectively (e.g. fatal illnesses).  
192 Furthermore, by allowing a wide range of different conditions to be studied within the same  
193 study population, the full effects of a particular exposure on all aspects of health can be better

194 assessed (e.g. smoking on a wide range of different diseases). Likewise, the effects of many  
195 different exposures on a single disease can be determined, provided that sufficient numbers  
196 of cases have occurred to allow the separate and combined effects of exposures to be  
197 assessed reliably.

198         Prospective studies need to be large, as only a relatively small proportion of the  
199 participants will develop any given condition during follow-up. The rationale for recruiting  
200 500,000 adults into UK Biobank was that it would enable large numbers of cases of the most  
201 common diseases to develop within a reasonable follow-up period (while also allowing detailed  
202 exposure information to be collected within funding and organisational constraints). For  
203 example, after a median follow-up of 12 years (i.e. by end-2020), linkage to electronic  
204 healthcare record data indicated that there had been at least 30,000 incident cases of  
205 diabetes, 25,000 cases of depression, 15,000 cases of myocardial infarction, and 10,000  
206 cases of breast cancer (Table 1). For the reliable detection of risk ratios of about 1.3 for the  
207 main effects of different exposures (ranging from those that are dichotomous variables to  
208 those that are continuous measures), about 5,000-10,000 incident cases of a particular  
209 disease would be required (22). The need for a large sample size is even more evident when  
210 assessing combined effects. For example, when estimating the joint effect of blood pressure  
211 and age on the risk of coronary heart disease, the standard error of the estimates (and hence  
212 the 95% confidence intervals) are, on average, three times narrower with 500,000 versus  
213 50,000 participants (23). As the UK Biobank participants age, the number of incident cases of  
214 different diseases is increasing substantially, allowing a wider range of outcomes to be  
215 investigated more completely. For example, by 2032 there will be over 50,000 cases of  
216 diabetes and chronic obstructive pulmonary disease. The sheer size of the study also means  
217 that robust research into less common conditions will also be possible. For example, between  
218 2020 and 2027, the number of cases of Alzheimer's disease, hip fracture and Parkinson's  
219 disease is expected to more than double to about 17,000, 13,000 and 10,000, respectively  
220 (Table 1).

221 **Comparing cohort characteristics with that of the wider population**

222 In UK Biobank, the well-defined sampling frame means that it is possible to assess not  
223 just the overall participation rate, but also the extent to which the study population differs from  
224 the wider population from which it was drawn. Postal invitations were sent to 9.2 million  
225 individuals aged 40–69, who were registered with the UK’s National Health Service (NHS) and  
226 lived within a short travelling time (typically about 25 miles) of one of 22 dedicated assessment  
227 centers. The choice of their location was determined by population density, ease of access,  
228 and potential to reach certain types of participants (e.g. ethnic minority groups and those living  
229 in more socio-economically deprived areas). During 2006-2010, 502,000 participants were  
230 recruited (5.5% of those invited). Although the participation rate was low, and those who joined  
231 the study were somewhat healthier and wealthier than the UK population across the same age  
232 range (24), the cohort includes large numbers of individuals across a broad spectrum of risk  
233 factors (i.e. that vary from low to high exposure levels of a wide range of potential risk factors).

234 It is this heterogeneity across different levels of exposures (e.g., genetic, lifestyle,  
235 sociodemographic and environmental exposures) - and not the relatively low overall  
236 participation rate - that largely determines the generalisability of the findings to the broader  
237 UK population (25). For example, although individuals from more socio-economic deprived  
238 areas are under-represented in UK Biobank (16% versus 33% in the UK population), there  
239 are sufficiently large numbers of this group (82,000) to enable reliable assessment of the  
240 association of socio-economic deprivation with disease risk. By contrast, although UK Biobank  
241 is reasonably representative of the distribution for different ethnic groups, with 29,000  
242 participants recruited from Black and other ethnic minority groups (which was about the same  
243 proportion, ~5%, as the rest of the UK population at the time) (26), it is insufficient to examine  
244 reliably the differences in exposure-disease associations by ethnicity. Even though UK  
245 Biobank is currently the largest study in the world with whole-genome sequencing data on

246 individuals of African and South Asian ancestry (27), the numbers are still relatively small (with  
247 about 10,000 participants in each ethnic group).

248           Researchers who wish to present simple summary statistics (for example, means or  
249 proportions) using UK Biobank data that are representative of the underlying population could  
250 consider using sampling weights that reflect the population distribution of the variables under  
251 investigation, although such techniques have not been used widely. However, one research  
252 group found that standardisation of the prevalence of lifestyle factors with those derived from  
253 national survey data did not substantially alter the magnitude or direction of the association of  
254 lifestyle factors with mortality from cardiovascular disease or cancer (28). The one notable  
255 exception was an attenuation of the apparent protective association of alcohol with  
256 cardiovascular disease, which has been shown to be likely affected by bias (29).

257 There are circumstances where lack of representativeness may introduce bias, particularly if  
258 the risk factors of interest are related to study selection (an example of collider bias) (30). For  
259 example, UK Biobank participants are more likely to be non-smokers and to live in more  
260 affluent areas than the general population in the same age range. Given that area-level socio-  
261 economic deprivation is moderately inversely correlated both with participation in UK Biobank  
262 and lung cancer, this non-representativeness may attenuate the observed association of  
263 smoking with lung cancer if the effects of smoking and socio-economic deprivation are not  
264 independent or synergistic (31). Likewise, UK Biobank participants were more likely to use  
265 supplements and to have lower incident disease rates than the general population (at least in  
266 the early years of follow-up), leading to an apparent inverse association between glucosamine  
267 supplement usage and mortality (32). Analyses involving genetic variants that cluster by place  
268 of birth also have the potential to yield biased associations if standard variables such as  
269 assessment centre and ancestry-based principal components cannot completely correct for  
270 this latent structure (33). However, for most genetic analyses where confounding from other  
271 risk factors is likely low, selection bias would typically be expected to be modest.

272 Consequently, in the interpretation of all research findings – whether they arise from the UK  
273 Biobank study or other prospective studies – it is important to consider the extent to which  
274 they might be affected by selective participation (i.e., selection bias). Given that traditional  
275 methods of identifying and controlling for selection bias (and other types of bias) may not be  
276 adequate, graphical tools such as directed acyclic graphs may provide a useful visual  
277 representation of the underlying assumptions about the relationships between exposures,  
278 potential confounders, mediators, and outcomes, and how they relate to study participation  
279 (34). Sensitivity analyses that include factors correlated with participation (and ongoing  
280 engagement) as covariates in the exposure-disease model can be performed; probability  
281 weighting, simulations and multiple imputation can be used to explore the potential impact of  
282 missing values related to participation on effect estimates (31, 35).

283 The general consistency of research findings in UK Biobank with those in other studies (36-  
284 38) – in particular, studies considered to be representative of the underlying population –  
285 suggest that many of the exposure-disease associations found in UK Biobank are largely  
286 generalizable to other populations. For example, the direction and magnitude of associations  
287 of genetic variants with osteoarthritis in UK Biobank are consistent with the associations  
288 observed in deCODE, which recruited more than half of Iceland’s adult population (39).  
289 Likewise, although the frequency of genetic variants may vary substantially in studies  
290 conducted in different populations (resulting in differing statistical power to detect  
291 associations), the direction and magnitude of genetic associations are typically similar across  
292 populations e.g. the association of specific *GPR75* gene variants with obesity in UK, US and  
293 Mexico cohorts (40).

294 Nonetheless, there may be circumstances in which associations between an exposure and  
295 disease risk varies across different populations. For example, polygenic risk scores developed  
296 and tested in populations of European ancestry often perform less well when applied to African  
297 and South Asian populations, owing to differences in allele frequencies and linkage

298 disequilibrium patterns between the ethnic groups (41). As such, other large population  
299 cohorts with biological samples are needed around the world to increase the heterogeneity of  
300 genetic and non-genetic risk factors for disease (42) (Table 2). For example, studies  
301 established in Mexico (150,000 participants) and China (500,000 participants) at about the  
302 same time as UK Biobank have enabled reliable investigation into the association between  
303 the risk of hypertension with body weight above and below the Western norm (43, 44). Large-  
304 scale studies established across Europe and China have also taken advantage of the  
305 heterogeneity of dietary and other exposures across different populations (45,46). Genetic  
306 and other assays of stored samples in these studies are extending the range of genomic risk  
307 factors that can now be investigated. New large-scale prospective studies are now established  
308 in the US e.g., All of Us (47) and the Million Veterans Program (48), and are also being  
309 established in Asia and parts of Africa e.g., Non-communicable Diseases Genetic Heritage  
310 Study in Nigeria (49, 50). This will further increase the ability to assess associations with  
311 disease risk across a broad range of genetic (and non-genetic) factors as long as there is  
312 sufficient duration of follow-up.

### 313 **Reliable assessment of a wide range of exposures**

314 The inclusion of participants exposed to different levels of risk factors (e.g. ranging from low  
315 to high intake of different dietary factors, smoking, sun exposure, etc.) is of value in assessing  
316 the generalisability of findings, which is enhanced further by analyses across studies  
317 established in different populations. However, all observational studies face challenges of  
318 exposure measurement error, in which risk factors and their potential confounders are  
319 measured imperfectly or incompletely, thereby introducing both random error (when  
320 measurements fluctuate randomly around their true value) and systematic error (when  
321 measurements vary in the extent to which they are higher or lower than their true value).

322 As a result, UK Biobank has put significant effort into collecting comprehensive, accurate and  
323 high-quality data for many different types of exposures. Repeated measures have also been

324 conducted in subsets of participants to address random error in exposure levels and thereby  
325 be able to correct for regression-dilution bias. However, there is real value in being able to  
326 perform cohort-wide repeat measures that would allow the relevance of individual changes in  
327 exposures over time to be assessed.

### 328 **Depth and breadth of exposure measurement**

329 In UK Biobank, a wide range of questionnaires and physical devices (e.g. spirometer to  
330 measure lung function, sphygmomanometer to measure blood pressure, bioimpedance device  
331 to measure body composition, dynamometer to measure hand grip strength, etc.) have been  
332 used (Fig. 1) to collect data that are reliable, valid and of high scientific value (26, 51); such  
333 data continue to be collected and extended. During recruitment, UK Biobank used touch-  
334 screen and computer-assisted personal interview direct data-entry systems (instead of paper-  
335 based approaches that were routinely used at the time in such studies), as well as direct data  
336 transfer from measurement devices. This strategy enhanced data accuracy and completeness  
337 by supporting automated real-time consistency checks and data quality monitoring to identify  
338 and correct errors. Participants were also asked to bring certain information (e.g. medications,  
339 operations, family history, and birth details) to reduce errors associated with memory recall.  
340 However, perhaps the greatest benefit of using a touch-screen data entry model was that it  
341 reduced the time taken to collect data and thereby enabled a greater range of potential risk  
342 factors for disease to be collected. For example, data on sociodemographic factors (income,  
343 education, occupation), ethnicity, family history, lifestyle (diet, alcohol consumption, smoking  
344 history, physical activity, sleep, sun exposure, sexual history), early life factors, psychosocial  
345 factors, medical history, cognition and environmental exposures were all collected via the  
346 touch-screen questionnaire in about fifty minutes.

347 A wide range of physical measurements were also taken for all 500,000 participants,  
348 comprising blood pressure, anthropometry (sitting and standing height, weight, waist and hip  
349 circumference, and bioimpedance measures), hand grip strength, vision and lung function.

350 Blood and urine samples were also collected for long-term storage (Fig. 1). A proportion of the  
351 cohort also underwent a heel ultrasound for bone density, pulse wave velocity of arterial  
352 stiffness, a hearing test (180,000 participants), an eye examination (including refractive index),  
353 intraocular pressure measurements, a retinal photograph and optical coherence tomography  
354 (120,000 participants), a cardio-respiratory fitness test with a 4-lead electrocardiogram (ECG)  
355 (78,000 participants), and collection of a saliva sample (~85,000 participants). Since the  
356 baseline assessment, UK Biobank continues to collect additional data from large subsets of  
357 the cohort. This has included data on physical activity using a 7-day accelerometer (in 100,000  
358 participants, with 2,500 undergoing a repeat assessment), a multi-modal imaging assessment  
359 (in up to 100,000 participants, with 60,000 undergoing a repeat assessment over the next few  
360 years) and a series of web-based questionnaires that cover specific exposures in more depth  
361 (e.g. diet, cognition, occupational history).

362 Rigorous approaches have also been taken to sample collection, processing, retrieval and  
363 assay measurement. Prior to the start of UK Biobank, a series of pilot studies were conducted  
364 to determine the optimal method for sample collection and processing (52), followed by the  
365 development of a state-of-the-art robotic system and sample tracking software to ensure  
366 consistency of sample processing. Currently, genomic data (genome-wide genotyping and  
367 imputation, whole-exome and whole-genome sequence data, telomere length), as well as  
368 hematological and biochemical data are available for the whole cohort (Fig. 1). UK Biobank's  
369 general policy of performing cohort-wide assays supports research into a wide number of  
370 conditions and helps to avoid measurement errors that would otherwise occur with different  
371 assay methods, reagents and equipment in different laboratories used in different subsets of  
372 the cohort at different times. To facilitate quality control, algorithms were developed to retrieve  
373 sample aliquots in a sequence that avoided clustering by recruitment location, date or time of  
374 day (53). Consequently, when assaying samples from participants in this quasi-random order,  
375 the mean biomarker concentration across batches and analysers should be constant, which  
376 allows correction for variation caused by laboratory drift. Throughout the assay process, the



377 data are reviewed to identify issues and either address them in real time (e.g., if specific  
378 batches require re-measurement) or make any adjustments retrospectively. For example,  
379 following assay measurements of blood biochemistry markers, these data were corrected for  
380 systematic error caused by unexpected dilution that occurred in some aliquots during sample  
381 processing (53). Moreover, the use of highly efficient assay methods minimises sample  
382 depletion (with currently less than 10% of the baseline blood sample used so far), which will  
383 allow other types of assays (e.g., epigenetics, transcriptomics and proteomics) to be  
384 conducted on a cohort-wide basis when technological advances make this possible.

385 The collection of different types of data that describe the same (or highly related) exposures  
386 can also contribute to accuracy. In particular, a more precise assessment performed in a  
387 subset of participants could be used to correct for any random and systematic error inherent  
388 in the less precise baseline measures conducted in the full cohort (54). For example, data  
389 from an accelerometer device worn by 100,000 UK Biobank participants was used to calibrate  
390 self-reported physical activity estimates provided by all 500,000 participants at recruitment  
391 (55). Similarly, data on body fat composition available from dual-energy x-ray absorptiometry  
392 scans (56), which are being collected in up to 100,000 participants attending an imaging  
393 assessment, can be used to calibrate the bio-impedance measures available from the full  
394 cohort. Detailed dietary data from web-based questionnaires collected in over 200,000  
395 participants can also be used to predict food and nutrient intake for the entire cohort, as  
396 demonstrated in other studies (54).

397 The collection of data on a wide range of measures enables researchers to allow not only for  
398 more complete and accurate measurement of exposures, but also for potential confounders  
399 (extraneous factors that are associated with the exposure and outcome) and mediators  
400 (factors that are on the causal pathway between the exposure and the outcome). This is  
401 important, as random error in exposure measures can cause systematic attenuation of any  
402 true association, whereas random measurement error of confounders can result in an

403 apparent exposure-disease association, where none really exists. For example, the observed  
404 inverse association of fruit and vegetable intake with cardiovascular disease risk in UK  
405 Biobank is likely to be due largely to residual confounding by socio-economic factors, which  
406 are difficult to assess and therefore subject to measurement error (57). The ability of UK  
407 Biobank to obtain more detailed information in the future about socio-economic factors (such  
408 as education, occupation and income via linkage to administrative datasets or specific web-  
409 based questionnaires) would enable more precise characterisation and, hence, even better  
410 adjustment for these important factors.

411 Because all epidemiological studies suffer, to a greater or lesser extent, from imperfect  
412 measurement of exposures and their potential confounders, various analytical methods have  
413 been developed to quantify and control for this. Perhaps the simplest approach is the  
414 comparison of likelihood ratio statistics associated with the exposure of interest in the models  
415 before and after adjustment for covariates. Generally speaking, a large proportional reduction  
416 in the likelihood ratio chi-square ( $LR\chi^2$ ) test after the addition to the model of covariates is  
417 indicative that the association likely remains affected by residual confounding, as adjustment  
418 for confounders that are perfectly measured would be expected to reduce the  $\chi^2$  even further  
419 (6). An increasingly popular approach to distinguish the likely causal effect of an exposure  
420 (from that of extraneous confounders) is the use of Mendelian Randomisation – facilitated in  
421 analyses of UK Biobank by the extensive genetic information available on all of the participants  
422 – whereby specific genetic variants are used as proxies for exposures of interest or their  
423 confounders. For example, this approach has provided strong support for a causal role of body  
424 fat mass and interleukin-6 in development of cardiovascular conditions (58, 59). Conversely,  
425 Mendelian Randomisation has not provided support for a protective effect of vitamin D against  
426 COVID-19 (60), cancer or cardiovascular outcomes (61), although it should be noted that  
427 Mendelian Randomisation analyses may also be affected by bias in some circumstances (62).  
428 When associations of genetic variants with the relevant non-genetic risk factors are weak  
429 (such that Mendelian Randomisation may not be effective), the likely impact of residual

430 confounding due to imprecision in measured variables included in the model can be assessed  
431 using other analytical approaches such as probabilistic or multiple-bias analysis (34, 63). The  
432 use of different analytical strategies to triangulate evidence (for example, comparing results  
433 from models that include traditional observational variables with those that use genetic  
434 instrumental variables) will enable researchers to assess different biases and their potential  
435 impact on causal inference in a more robust manner.

#### 436 **Repeated exposure measurements**

437 Random errors in the measurement of risk factors can lead to substantial underestimation of  
438 the strength of their associations with subsequent health outcomes (regression dilution bias)  
439 (64, 65), as well as to substantial residual confounding when measurement error is present in  
440 confounders (66). These biases may be increased further through random error in risk factor  
441 measurements that occur during prolonged follow-up in prospective cohorts. For example, the  
442 true association of blood pressure and cholesterol with cardiovascular disease risk may be  
443 underestimated by about one-third in the first decade of follow-up and up to two-thirds in the  
444 third decade (64). However, despite regression dilution being one of the most important biases  
445 in exposure-disease associations, it is often overlooked in analyses of prospective studies,  
446 including UK Biobank (with some exceptions) (67-70). It is possible to correct for regression  
447 dilution bias by using repeat measures from a relatively small subset of the cohort. UK Biobank  
448 performed a repeat assessment on 20,000 participants in 2012-2013 to allow researchers to  
449 address this issue specifically. Re-measures collected during the imaging assessment of up  
450 to 100,000 UK Biobank participants during 2014-2024 and a repeat assessment of up to  
451 60,000 during 2019-2029 can be used to make appropriate time-dependent corrections for the  
452 effects of regression dilution bias.

453 In addition to addressing error caused (largely) by random error in baseline risk factors,  
454 repeated measures would also enable correction for systematic intra-individual changes in

455 exposures over time, which may lead to either over-estimation or under-estimation of  
456 associations depending on the nature and magnitude of misclassification. For example,  
457 secular trends in the reduction of smoking or exposure to environmental pollutants may lead  
458 to an underestimation of their association with disease risk if solely based on baseline  
459 measures. To help address this issue, UK Biobank is exploring opportunities to collect  
460 information on longitudinal changes in environmental exposures (e.g. from existing data on  
461 changes in participants' residential location or future data collection using smartphone GPS  
462 tracking) to enable more accurate inferences to be made about how changes in environmental  
463 exposures affect health in the long-term. It is also intended to repeat previous web-based  
464 questionnaires in order to capture longitudinal changes in specific lifestyle factors such as diet  
465 and sleep.

466 Whereas repeated measures of the baseline assessment are being captured during the  
467 imaging assessments in a subset of the UK Biobank cohort, it would be desirable to perform  
468 a future repeat assessment of a wide range of exposures in as many of the participants as  
469 possible. This would allow investigation of how lifestyle, and physical and biochemical  
470 changes over time influence disease risk and progression, thereby helping to determine the  
471 temporality of associations and their underlying mechanisms. Data collection for as many  
472 surviving participants as possible would also reduce systematic error caused by differential  
473 participation rates that are related to the exposures and outcomes under investigation. UK  
474 Biobank generally has excellent participant engagement with an ongoing series of repeated  
475 web-based questionnaires (with response rates of >50%), physical activity monitoring (45%  
476 for the first assessment, of whom 63% also performed a repeat assessment), and imaging  
477 assessments (24% for the first assessment and 65% for a repeat assessment). However,  
478 researchers should be aware that participants who engage in ongoing data collection activities  
479 (including repeat assessments) might not be representative of the cohort as a whole. For  
480 example, genetic variants associated with completing UK Biobank online questionnaires and  
481 activity monitoring are correlated with several metrics of better health (31). Attrition bias has

482 been documented in other prospective studies (71-73), suggesting that similar factors affect  
483 ongoing participant engagement in many cohorts, regardless of their design, recruitment  
484 strategy or study population.

#### 485 **Reliable assessment of a wide range of health outcomes**

486 To minimise bias in exposure-disease associations, it is important that health outcomes are  
487 identified in a comprehensive manner and in as much detail as possible. Linkage to routine  
488 electronic health records, supplemented with information from self-reported questionnaires  
489 and other remote methods, and in-person assessments focused on specific outcomes (such  
490 as dementia), will help to deeply characterise health outcomes that are of high priority. The  
491 ability to combine these data from disparate sources to generate 'off-the-shelf' outcomes that  
492 can be easily interpreted by non-specialists will further increase the usability and  
493 reproducibility of research using these data.

#### 494 **Comprehensive ascertainment of health outcomes**

495 All cohort studies need a comprehensive and efficient way of following participants' health  
496 over the long-term to identify a wide range of disease outcomes. Unlike many countries  
497 (including the US and most low-to-middle income countries), the UK's National Health Service  
498 (NHS) collates and stores electronic health administrative records for clinical care. However,  
499 the data content, format and governance requirements may differ for England, Wales and  
500 Scotland. To identify a wide range of health outcomes over a prolonged period, UK Biobank  
501 has linked to these health administrative records for all participants. This has the advantage  
502 of minimising ascertainment bias and reducing loss-to-follow-up or attrition bias by providing  
503 cohort-wide follow-up information without the need for active participant re-contact, which may  
504 be incomplete. Moreover, the low rate of UK Biobank participants requesting that all of their  
505 data and samples be withdrawn from the study (0.2%; most of which occurred soon after

506 recruitment) also minimises systematic bias associated with loss to follow-up from non-  
507 random subgroups of the cohort.

508 To date, UK Biobank has linked NHS healthcare data from centralised national cancer and  
509 death registries and hospital inpatient admissions for all participants. In contrast, primary care  
510 data are not centralised but instead are held by commercial electronic system suppliers under  
511 the control of individual general practices, so it has been more challenging to obtain the  
512 agreements necessary to obtain these data for all participants. Primary care data are currently  
513 available for 45% of the UK Biobank cohort for general research purposes (which represents  
514 complete coverage from one primary care system supplier, up to 2016/2017) and for 80% of  
515 the cohort for COVID-19 research (complete coverage from two system suppliers in England,  
516 up to mid-2021, enabled by emergency legislation to facilitate COVID-19 research). Whereas  
517 both subsets are broadly representative of the cohort with respect to the distribution of potential  
518 exposures, researchers should be encouraged to check these underlying assumptions prior to  
519 analysis. Incorporation of primary care data for all 500,000 participants for all types of health-  
520 related research would be of enormous value as it will increase substantially the number of  
521 health outcomes that can be detected (thereby increasing statistical power) and their  
522 diagnostic accuracy (thereby increasing specificity). For example, whereas addition of primary  
523 care data would increase the numbers of myocardial infarction cases identified by less than  
524 5%, the numbers of cases identified of diabetes and chronic obstructive pulmonary disease  
525 (COPD) would increase by about 40% (Fig. 2). Primary care data are also important for  
526 investigating risk factors associated with disease severity, where associations may differ  
527 between milder disease subtypes generally captured in primary care records and more severe  
528 disease captured in hospital admission data.

529         Whereas linkage to health records ensures comprehensive coverage, there is the  
530 possibility of “collider bias” if health outcomes are differentially ascertained based on  
531 participant characteristics (e.g., ethnicity), as reported by some researchers in the context of  
532 COVID-19 research (74). However, there are a range of analytical approaches that can be

533 used to investigate this type of bias (74-76) and the ascertainment of most health outcomes  
534 are not so strongly influenced by these characteristics.

### 535 **Specificity of health outcomes**

536 Given that the prospective nature of cohort studies facilitates research into many diseases,  
537 the challenge is not only how to identify probable cases of disease but also to increase the  
538 precision and specificity of those diagnoses. The aim is to avoid a situation where insufficient  
539 data on health outcomes leads to misclassification of cases and non-cases, thereby reducing  
540 statistical power to detect an association. As such, UK Biobank's aim is to ascertain as many  
541 cases as possible (i.e., to achieve adequate sensitivity) while minimising the number of false-  
542 positive cases (i.e., achieving a high positive predictive value). It is worth recognising that it is  
543 not necessary to identify all cases of a disease as false negatives will be diluted by the much  
544 larger number of 'true' controls (and so have limited impact). To help identify as many cases  
545 as possible, UK Biobank administers various web-based questionnaires, developed in close  
546 collaboration with relevant experts, to collect data on health outcomes that are incompletely  
547 recorded in health records, such as depression and anxiety (77), and neurodevelopmental  
548 and gastrointestinal conditions.

549 It is also important to characterise disease subtypes as low biological specificity can limit  
550 interpretation of results. To address this, UK Biobank (78-80) and other open-access  
551 resources (81) have developed a number of algorithmically defined health outcomes based  
552 on inter-operable code lists from electronic healthcare records. Diagnostic codes contained in  
553 these records have also been mapped to a common standard (ICD-10) to facilitate broad-  
554 brush research. Whereas these coded health outcomes may be sufficient for most research  
555 purposes, they may lack specificity to identify disease subtypes. This could lead to materially  
556 biased estimates of associations if the determinants of these apparently similar, but  
557 etiologically different, disease subtypes differ. For example, while blood pressure is strongly

558 positively associated with the risk of both ischaemic and haemorrhagic stroke (82), the  
559 association of cholesterol and certain genetic variants with stroke differ substantially by  
560 subtype (83, 84) providing clues to the underlying aetiology of this heterogeneous condition.  
561 To increase the specificity of health outcomes beyond the available coded data, UK Biobank  
562 intends to collect detailed data on disease sub-types over the next few years. For example,  
563 this could include disease-specific registers such as the National Diabetes Audit that collects  
564 data on diabetes subtypes, clinical scans to identify stroke sub-types, digitised histopathology  
565 slides to determine tumour morphological subtypes, and in-person assessments to  
566 characterise dementia subtypes.

567 It is possible to identify some disease sub-types using other data already available in the UK  
568 Biobank resource. For example, biochemistry measures have been used to ascertain chronic  
569 kidney disease (85), MRI scans collected in up to 100,000 participants have been used to  
570 define dilated cardiomyopathy (86) and non-alcoholic fatty liver disease (87), and genetic data  
571 have been used to distinguish diabetes subtypes (88). However, researchers should be aware  
572 of the potential for generating misleading associations where the exposure of interest (e.g.  
573 genetic variants or biochemistry measures) has, in part, been used to define the outcome.

#### 574 **Long duration of follow-up**

575 For any prospective study, a long duration of follow-up (i.e. decades or more) is needed for  
576 sufficiently large numbers of health outcomes to accrue for reliable investigation. It also allows  
577 for the identification of recurring events and factors associated with disease progression. While  
578 the incidence of common health outcomes during the early years of follow-up in UK Biobank  
579 was somewhat lower than in the general population due to the 'healthy volunteer' effect, which  
580 is typical of such studies (89), its impact is now reduced as the cohort has aged. With  
581 prolonged follow-up, large numbers of incident cases of a wide range of conditions have  
582 already occurred. Over the next five to ten years there will be thousands of incident cases of



583 common outcomes (Table 1), enabling reliable investigation of their genetic, lifestyle and  
584 environmental determinants.

585 The rationale for recruiting middle-aged participants was to collect risk factor data many years  
586 before the development of any given condition, thereby minimising reverse causation bias.  
587 However, conditions that have a long prodromal phase (e.g. dementia or diabetes) or that can  
588 exist for years before a clinical diagnosis is made (such as prostate cancer) may affect the  
589 levels of risk factors measured at recruitment and create spurious associations. For example,  
590 associations observed between high insulin-like growth factor-I (IGF-I) concentrations and  
591 increased risks of cataract and diabetes were substantially attenuated after excluding the first  
592 five years of follow-up in UK Biobank (90), suggesting that baseline IGF-I concentrations may  
593 be altered as a result of early pathophysiological processes. Other large-scale longitudinal  
594 studies have also shown that apparent inverse associations between lifestyle factors and  
595 dementia risk are also likely to be due to reverse causation bias during the first 10-15 years of  
596 follow-up (91). Consequently, researchers should consider the impact of exclusion of  
597 participants with prevalent disease prior to analysis and perform sensitivity analyses to assess  
598 exposure-disease associations across different periods of follow-up to determine whether the  
599 first years of follow-up should be excluded (92).

## 600 **Conclusions**

601 The success of UK Biobank has been due, in large part, to the altruism of the 500,000  
602 volunteers, but also the global research community who have been – and continue to be –  
603 involved in expanding the range of exposures and outcomes available for research. Such  
604 enhancements (e.g. sample assays, linkage to specific healthcare datasets and environmental  
605 sources, etc.) help to ensure that the resource fulfils the needs of researchers and remains at  
606 the forefront of scientific discovery.

607 UK Biobank's large-scale prospective design and easy access to a wealth of genetic,  
608 phenotypic and health data provides a powerful resource to help address previously  
609 unanswerable questions of the determinants of incident disease, as well as enabling research  
610 into risk prediction and identification of early biomarkers of disease. Whereas the UK Biobank  
611 study has attempted to minimise random and systematic errors in the measurement of  
612 exposures and outcomes with good study design, researchers need to use the data in ways  
613 that best answer the questions posed, and to be aware of and, where necessary, use  
614 analytical methods to take account of potential biases when interpreting research findings.

615 Easy accessibility of UK Biobank data and research results (including the underlying analytical  
616 code) is enabling the community to directly peer review research by undertaking replication  
617 analyses, or to apply different methods to the same research question, to confirm or refute the  
618 findings of others. In particular, investigation of approaches used to identify and quantify the  
619 uncertainty of the results based on sensitivity analyses that examine systematic bias, will  
620 provide a level of transparency in the interpretation of findings that has, until now, generally  
621 been under-reported.

622 Whereas UK Biobank is well suited to address a wide range of health-related research  
623 questions, similar studies in other populations with different ranges of exposures and  
624 outcomes are needed. Taken together, they will enable a greater range of risk factors and  
625 diseases to be analysed and allow for replication of associations, which is essential before  
626 determining the extent to which any specific research findings are generalizable to different  
627 populations. Scientific discoveries benefit from the availability of data from diverse populations  
628 that cover a wide range of the many different genetic, ancestral, ethnic, lifestyle and  
629 environmental factors that may influence risk of a broad range of diseases.

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**Table 1. Cumulative numbers of observed (2020) and predicted incident cases of various health conditions**

Condition	Year of diagnosis		
	Observed <sup>1</sup>	Predicted	
	2020	2027	2032
Diabetes	31,000	54,000	70,000
Myocardial infarction	15,000	30,000	46,000
Stroke	12,000	25,000	37,000
COPD	25,000	47,000	65,000
Depression	25,000	39,000	47,000
Breast cancer	9,000	14,000	18,000
Colorectal cancer	5,000	8,000	11,000
Lung cancer	4,000	6,000	8,000
Prostate cancer	10,000	16,000	20,000
Hip fracture	5,000	13,000	22,000
Rheumatoid arthritis	4,000	6,000	8,000
Alzheimer's disease	5,000	17,000	37,000
Parkinson's disease	4,000	10,000	14,000

<sup>1</sup> Observed values are based on incident events identified from linkage to records of deaths, hospitalisations, cancers, and primary care in the cohort to the end of 2020.

**Table 2. Sampling characteristics of selected general population prospective studies with at least 250,000 participants, containing genomic, behavioural and health outcome data<sup>1</sup>**

<b>Study name</b>	<b>Recruitment dates (range)</b>	<b>Location</b>	<b>Sample size</b>	<b>Sex; Age at recruitment</b>	<b>Population from which the sample was recruited</b>	<b>Participation rate</b>
23andMe ( <a href="http://www.23andme.com">www.23andme.com</a> )	2007 - present	Global (but mainly USA)	6.8M	MF; 13+	Customers of a personal genetics company	not known
45 and Up (93)	2006 - 2009	Australia	267,000	MF; 45+	New South Wales residents enrolled in Medicare, recruited through direct invitations	19%
All of Us (47)	2018 - present	USA	Ongoing. Aim: 1M	MF; 18+	Varied approaches, many of which are targeted at underrepresented groups via direct and indirect means	not known
Canadian Partnership for Tomorrow's Health (CanPath) (94)	2008 - present	Canada	330,000	MF; 30-74	Residents across Canada recruited into 7 regional cohorts using varied approaches	not known

China Kadoorie Biobank (46)	2004 - 2008	China	510,000	MF; 30-70	Residents of 10 geographically defined regions across China, recruited through direct invitations	30%
European Prospective Investigation into Cancer, Chronic Diseases, Nutrition and Lifestyle (EPIC) (45)	1992 - 2000	10 European countries	520,000	MF; 35-70	Residents from 23 centres located in 10 European countries recruited through direct invitations	not known
Kaiser Permanente Research Bank (95)	2007 – 2013	USA	400,000	MF; 18+	Members of Kaiser Permanente health plan recruited through direct invitations, in-person communication and via website.	20-50% of each areas' insured population
Million Veterans Program (48)	2011 - present	USA	Ongoing. Aim: 1M	MF; 18+	Members of the Veterans Health Administration System recruited through direct invitations and indirect (promotional materials) methods	14%
UK Biobank (26)	2006 - 2010	UK	500,000	MF: 40-69	Residents living close to 22 assessment centres in the UK, recruited via direct invitations	5.5%

<sup>1</sup> The IHCC (<https://ihccglobal.org/>) has details of other prospective studies of less than 250,000 participants



## **Figure legends**

**Fig. 1. Illustration of the types of data collected in UK Biobank, which includes data collected at in-person assessments (e.g. lifestyle factors, medical history, blood pressure and other physical measures, imaging scans), data from online questionnaires, data generated from biological samples and data from electronic healthcare records over time**

**Fig. 2. The proportion of incident cases (i.e. ascertained since recruitment into the study) identified through hospital inpatient admissions, primary care and death data for some common exemplar conditions (myocardial infarction, diabetes and chronic obstructive pulmonary disease)**