DATA NOTE

An overview of the TwinsUK cohort’s anxiety and depression assessment, using the self-reported Hospital Anxiety and Depression Scale [version 1; peer review: 2 approved with reservations]

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Abstract

Anxiety and depression are common mental health conditions that frequently coexist. The Hospital Anxiety and Depression (HADS) questionnaire, is a widely used questionnaire, both in the clinic and in research. HADS provides an assessment of anxiety and depression based on non-physical symptoms, hence it can be used in patients with other physical pain and symptoms. This resource provides an overview of all the HADS questionnaires completed by the twins in the TwinsUK registry. This includes both monozygotic and dizygotic twins, over a wide range of age and socioeconomic backgrounds. TwinsUK holds a wide range of phenotype and genotyping data that can be used as confounding factors in the study of mental health.

Keywords

TwinsUK, HADS, Mental Health, Anxiety, Depression, Stress disorder, The Hospital Anxiety and Depression Scale
Introduction

The UK Adult Twin Registry (or TwinsUK) is a cohort of volunteer adult twins currently consisting of 14,575 adult twins (55% monozygotic and 43% dizygotic) aged between 18 to 101 years from around the United Kingdom. The registry was started in 1992 through media campaigns targeted at middle-aged women to allow the investigation of osteoporosis and osteoarthritis. The success of early studies led to the expansion of the registry, and it now incorporates both male and female twins with a range of clinical and behavioral phenotypes as well as genotyping data.

The Department of Twin Research and Genetic Epidemiology at St. Thomas’ Hospital, King’s College London hosts the registry. The primary focus of study has been the genetic basis of complex diseases (cardiovascular, metabolic, musculoskeletal, and ophthalmologic diseases), which has broadened to include the complex healthy ageing process. The registry includes self-reported and clinical data that has been measured longitudinally for majority of volunteers through comprehensive visits, annual questionnaires, and several project-led studies. Figure 1 gives an overview of the primary and the first two follow-up visits in the TwinsUK cohort.

The second follow-up visits were part of the Healthy Aging Twin study that examined genetic and lifestyle factors that influence ageing over time. This was followed by a third cycle of follow up visits carried out between 2012 and 2017 in which 5286 individuals attended the clinics as part of the Biomedical Research Centre (BRC) study with volunteers from the TwinsUK registry, and over 6300 questionnaires were returned. The BRC study had aimed to understand the interactions between genes and environment in disease processes.

Here, we present the key variables available on this cohort with respect to depression and anxiety for use by the scientific community. The registry incorporates a range of other longitudinal data based on different self-reported questionnaires, follow up visits, and multi-omics assays, which can be combined with the dataset described. In total, 6432 of the individuals in the registry have at least one or more follow-up visit, with a mean follow-up time of 5.98 years. The general format of the visits were similar, and in all visits blood and urine samples were collected. Prior to the visits, participants completed a questionnaire focused on lifestyle, behavior, and a number of recent self-reported clinical findings. During the visits, a number of other tests, such as weight, height, blood pressure, grip strength, and biochemical levels, were measured. Cognitive tests such as the Cambridge Neuropsychological Test Automated Battery (CANTAB) were also performed in a subset of visits. As well as the self-reported and measured phenotypes mentioned above, TwinsUK also benefits from a number of genotyping and ‘omics’ data. These results are only available for a subsection of cohort. In the following sections of this
document the overlap between the ‘omics’ data and the HADS responses are provided.

We collected data on depression, anxiety and anxiety sensitivity in the TwinsUK population in order to understand the genetic epidemiology of these traits and their relation to other health related phenotypes and multi-omic measures collected on the cohort. These data are intended to enhance the health phenotyping in this population for the benefit of the scientific community and the public.

Methods
The Hospital Anxiety and Depression Scale (HADS) was devised by Zigmond and Snaith\[^3\]. It is a 14-item scale used to detect the level of anxiety and depression in a medical outpatient clinic setting. The HADS scale was included in the annual DTR Twin Health questionnaire in 2006 and more recently it has been sent to the twins as a supplement to the Baseline Health Questionnaire in 2017.

The completed and returned questionnaires from both batches have been merged and the data is presented in this dataset. Overall a total of 9227 questionnaires have been completed and returned from which 5169 were returned in 2006 and 4058 in 2017.

A total of 2470 individuals have more than one response time point while the rest only completed the questionnaire in one occasion. The majority of respondents (87.9%; \(N_f=5940\)) were female and 12.1% (\(N_m=814\)) were male.

The 14 items are listed below:

Q7_162. I feel tense or wound up (Table 1).
Q7_163. I still enjoy the things I used to enjoy (Table 2).
Q7_164. I get a sort of frightened feeling as if something awful is about to happen (Table 3).
Q7_165. I can laugh and see the funny side of things (Table 4).
Q7_166. Worrying thoughts go through my mind (Table 5).
Q7_167. I feel cheerful (Table 6).
Q7_168. I can sit at ease and feel relaxed (Table 7).
Q7_169. I feel as if I am slowed down (Table 8).
Q7_170. I get a sort of frightened feeling like butterflies in my stomach (Table 9).
Q7_171. I have lost interest in my appearance (Table 10).
Q7_172. I feel restless as if I have to be on the move (Table 11).
Q7_173. I look forward with enjoyment to things (Table 12).
Q7_174. I get sudden feelings of panic (Table 13).
Q7_175. I can enjoy a good book or radio, TV programme (Table 14).
Table 5. Q7_166. How often worrying thoughts go through the respondent’s mind.

| Answer                          | Frequency | Percent | Cumulative percent |
|--------------------------------|-----------|---------|--------------------|
| 0 Only occasionally             | 3445      | 37.6    | 37.6               |
| 1 From time to time, but not too often | 3913      | 42.7    | 80.3               |
| 2 A lot of the time             | 1309      | 14.3    | 94.6               |
| 3 A great deal of the time      | 492       | 5.4     | 100.0              |
| 999905*                         | 2         | .0      | 100.0              |
| Total                           | 9161      | 100.0   |                    |

*999905= Unable to determine the response given.

Table 6. Q7_167. How often the respondent feels cheerful.

| Answer                         | Frequency | Percent | Cumulative percent |
|-------------------------------|-----------|---------|--------------------|
| 0 Most of the time            | 6501      | 71.4    | 71.4               |
| 1 Sometimes                   | 2236      | 24.5    | 95.9               |
| 2 Not often                   | 317       | 3.5     | 99.4               |
| 3 Not at all                  | 54        | .6      | 100.0              |
| 999905*                       | 2         | .0      | 100.0              |
| Total                         | 9110      | 100.0   |                    |

*999905= Unable to determine the response given.

Table 7. Q7_168. If the respondent can sit at ease and relax.

| Answer                         | Frequency | Percent | Cumulative percent |
|-------------------------------|-----------|---------|--------------------|
| 0 Definitely                  | 2847      | 31.1    | 31.1               |
| 1 Usually                     | 4878      | 53.3    | 84.4               |
| 2 Not often                   | 1313      | 14.4    | 98.8               |
| 3 Not at all                  | 108       | 1.2     | 100.0              |
| 999905*                       | 2         | .0      | 100.0              |
| Total                         | 9148      | 100.0   |                    |

*999905= Unable to determine the response given.

Table 8. Q7_169. How often the respondent feels like they are slowed down.

| Answer                         | Frequency | Percent | Cumulative percent |
|-------------------------------|-----------|---------|--------------------|
| 0 Not at all                  | 2462      | 27.0    | 27.0               |
| 1 Sometimes                   | 5016      | 55.0    | 82.0               |
| 2 Very often                  | 1256      | 13.8    | 95.7               |
| 3 Nearly all the time         | 388       | 4.3     | 100.0              |
| 999905*                       | 1         | .0      | 100.0              |
| Total                         | 9123      | 100.0   |                    |

*999905= Unable to determine the response given.

Table 9. Q7_170. How often the respondent gets a sort of frightened feeling like butterflies in the stomach.

| Answer                         | Frequency | Percent | Cumulative percent |
|-------------------------------|-----------|---------|--------------------|
| 0 Not at all                  | 4155      | 45.4    | 45.4               |
| 1 Occasionally                | 4238      | 46.4    | 91.8               |
| 2 Quite often                 | 623       | 6.8     | 98.6               |
| 3 Very often                  | 125       | 1.4     | 100.0              |
| 999905*                       | 1         | 0.0     | 100.0              |
| Total                         | 9142      | 100.0   |                    |

*999905= Unable to determine the response given.

Table 10. Q7_171. If the respondent has lost interest in their appearance.

| Answer                          | Frequency | Percent | Cumulative percent |
|--------------------------------|-----------|---------|--------------------|
| 0 I take just as much care as ever | 6139      | 67.2    | 67.2               |
| 1 I may not take quite as much care | 2095      | 22.9    | 90.1               |
| 2 I don’t take as much care as I should | 820       | 9.0     | 99.1               |
| 3 Definitely                   | 79        | 0.9     | 100.0              |
| 999905*                       | 1         | 0.0     | 100.0              |
| Total                         | 9134      | 100.0   |                    |

*999905= Unable to determine the response given.

Table 11. Q7_172. How much the respondent feels restless as if she/he has to be on the move.

| Answer                         | Frequency | Percent | Cumulative percent |
|-------------------------------|-----------|---------|--------------------|
| 0 Not at all                  | 1524      | 16.7    | 16.7               |
| 1 Not very much               | 2700      | 29.6    | 46.2               |
| 2 Quite a lot                 | 3022      | 33.1    | 79.3               |
| 3 Very much indeed            | 1888      | 20.7    | 100.0              |
| 999905*                       | 3         | 0.0     | 100.0              |
| Total                         | 9137      | 100.0   |                    |

The total number of valid and missing responses for each phenotype is provided in Table 15.

The questionnaire can be divided in two categories of anxiety and depression. The items on the questionnaire that relate to anxiety are: Q7_162, Q7_164, Q7_166, Q7_168, Q7_170, Q7_172, Q7_174, and the items that relate to depression are: Q7_163, Q7_165, Q7_167, Q7_169, Q7_171, Q7_173, Q7_175.
**Scoring system**

The respondent is required to rate each item by selecting one of four responses (0, 1, 2, and 3). The score for anxiety and depression is calculated separately. An individual’s anxiety score is the sum of the scores on the anxiety related items and his/her depression score is the sum of depression-relate items. Table 16, provides the HADS scoring as well as the mean age and the male to female ratio amongst the respondents.

**Table 12. Q7_173.** How much does the respondent looks forward with enjoyment to things.

| Answer                                | Frequency | Percent | Cumulative percent |
|---------------------------------------|-----------|---------|--------------------|
| 0 As much as I ever did               | 3218      | 35.2    | 35.2               |
| 1 Rather less than I used to          | 1819      | 19.9    | 55.1               |
| 2 Definitely less than I used to      | 1296      | 14.2    | 69.2               |
| 3 Hardly at all                       | 2813      | 30.7    | 100.0              |
| 999905*                               | 2         | 0.0     | 100.0              |
| Total                                 | 9148      | 100.0   |                    |

*999905* = Unable to determine the response given.

**Table 13. Q7_174.** How often the respondent gets sudden feelings of panic.

| Answer                                | Frequency | Percent | Cumulative percent |
|---------------------------------------|-----------|---------|--------------------|
| 0 Not at all                          | 4835      | 53.1    | 53.1               |
| 1 Not very often                      | 3301      | 36.2    | 89.3               |
| 2 Quite often                         | 819       | 9.0     | 98.3               |
| 3 Very often indeed                   | 154       | 1.7     | 100.0              |
| 999905*                               | 2         | 0.0     | 100.0              |
| Total                                 | 9111      | 100.0   |                    |

*999905* = Unable to determine the response given.

**Table 14. Q7_175.** How often the respondent enjoys a good book or radio or TV program.

| Answer                                | Frequency | Percent | Cumulative percent |
|---------------------------------------|-----------|---------|--------------------|
| 0 Often                               | 7321      | 80.0    | 80.0               |
| 1 Sometimes                           | 1532      | 16.7    | 96.7               |
| 2 Not often                           | 218       | 2.4     | 99.1               |
| 3 Very seldom                         | 81        | 0.9     | 100.0              |
| 999905*                               | 1         | 0.0     | 100.0              |
| Total                                 | 9153      | 100.0   |                    |

*999905* = Unable to determine the response given.

**Table 15. Valid and missing responses.**

| Question | Valid (%) | Missing (%) |
|----------|-----------|-------------|
| Q7_162   | 9159 (99.3) | 68 (0.7)    |
| Q7_163   | 9182 (99.5) | 45 (0.5)    |
| Q7_164   | 9167 (99.3) | 60 (0.7)    |
| Q7_165   | 9186 (99.6) | 41 (0.4)    |
| Q7_166   | 9161 (99.3) | 66 (0.7)    |
| Q7_167   | 9110 (98.7) | 117 (1.3)   |
| Q7_168   | 9148 (99.1) | 79 (0.9)    |
| Q7_169   | 9123 (98.9) | 104 (1.1)   |
| Q7_170   | 9142 (99.1) | 85 (0.9)    |
| Q7_171   | 9134 (99.0) | 93 (1.0)    |
| Q7_172   | 9137 (99.0) | 90 (1.0)    |
| Q7_173   | 9148 (99.1) | 79 (0.9)    |
| Q7_174   | 9111 (98.7) | 117 (1.3)   |
| Q7_175   | 9153 (99.2) | 74 (0.8)    |

**Table 16. HADS scoring.**

| Variable   | Total Number | Mean Age | F:M ratio     |
|------------|--------------|----------|---------------|
| Anxiety    |              |          |               |
| Normal     | 6433         | 56.93    | 5675:758      |
| Borderline | 1667         | 54.24    | 1513:154      |
| Abnormal   | 1064         | 50.73    | 976:88        |
| Depression |              |          |               |
| Normal     | 8124         | 55.87    | 1808:223      |
| Borderline | 807          | 55.34    | 240:29        |
| Abnormal   | 254          | 53.49    | 231:23        |

The total scores are categorised as followed:

- 0–7 = Normal
- 8–10 = Borderline abnormal (borderline case)
- 11–21 = Abnormal (case)

**Omens data**

TwinsUK registry hosts a variety of clinical and self-reported phenotypes that can be used as confounding factors alongside the HADS dataset depending on the research project, some of these include, socioeconomic data, smoking, alcohol, and a number of cognitive phenotypes. Furthermore, there are a number of genetic, epigenetic, and ‘omics’ data that are available for subsets of participants. Table 17 gives the number overlap between the participants in this dataset and their omics data where available.
Table 17. TwinsUK ‘omics’ data.

| Novel Molecular and Genetic Phenotypes                                      | Number of overlap |
|---------------------------------------------------------------------------|-------------------|
| Genome-wide association study (Gwas)                                      | 3956              |
| Exome sequencing                                                          | 3307              |
| Epigenetic Methylated DNA immunoprecipitation sequencing (MeDIP-seq)      | 2821              |
| Metabolomics (Fasting Serum) Non-targeted metabolomic analysis using Metabolon Inc., platform. | 1849              |
| Glycomics                                                                 | 3387              |
| Microbiome gut (Gut flora DNA analysed with 16s sequencing technology)    | 2034              |
| Plasma Metals                                                             | 3157              |
| Salivary Metabolomics                                                     | 1851              |
| Faecal metabolomics                                                       | 868               |

Ethical approval and consent

All the data provided on this paper have been collected through questionnaires that had ethical approval as parts of Twins UK (EC04/015) or Healthy Ageing Twin Study (H.A.T.S) (07/ H0802/84) studies from Local Research Ethics Committee at the Department of Twin Research and Genetic Epidemiology, King’s College London. Written informed consent was obtained from all the TwinsUK volunteers upon registration and also during their clinical visits. All study members hold the right to withdraw their consent partially or entirely upon their request.

Data availability

TwinsUK facilitates and encourages the sharing of data with the scientific community to further scientific research. Researchers can follow the below steps to request and access the datasets provided on this data note as well as other TwinsUK data. All the datasets included in this data note can be accessed by quoting the data note name or specific variable codes provided within this report.

1. Please search for your required phenotype using the TwinsUK Phenotype spreadsheet containing a list of all TwinsUK phenotypes.
2. Please read the TwinsUK Data Access Policy document which describes the process of accessing the data and samples as well as the costs associated.
3. Please submit your Proposal Form to the TwinsUK Resource Executive Committee (TREC) for consideration. You will be notified of the outcome of the review within three weeks and advised on the next stage.

The proposal form should specify the data and/or samples required including individual variables with an appropriate justification describing the aims/hypothesis of the project for which the data is requested. Further information can also be found on the TwinsUK website (www.twinsuk.ac.uk/data-access). If you have any other enquires related to data access please email Collaborations and Data Access Manager, Victoria Vazquez (victoria.vazquez@kcl.ac.uk).

Grant information

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Simona Scaini
Sigmund Freud University Milan, Milan, Italy

- The aim of the report is not clear.
- Authors should clarify what they mean for genetic epidemiology (probably the definition genetic and environmental influences/contributions is more appropriate).
- More demographic details of the sample should be provided.
- Authors should provide information and comparisons on demographic information for participants vs non-participants.
- Please report data (on tables) for total sample as well as for MZ and DZ.

Is the rationale for creating the dataset(s) clearly described?
Partly

Are the protocols appropriate and is the work technically sound?
Yes

Are sufficient details of methods and materials provided to allow replication by others?
No

Are the datasets clearly presented in a useable and accessible format?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Psychological assessment and treatment in childhood and adolescence, Social and metacognitive competence development in childhood, Behavioral genetics in childhood and adolescence, Life events and developmental psychology and psychopathology, Psychobiology of anxiety in childhood
I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 20 May 2019

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Maj Vinberg
Department of Psychiatry, University of Copenhagen, Copenhagen, Denmark

Using twins in order to understand the genetic epidemiology of these traits, it is more correct to write the genetic contribution.

- Please describe the aim of the present report.
- Is the present twin sample representative for twin samples in general?
- Describe mean age and a description of participants vs. non-participants at follow-up would provide valuable information.
- How are cognitive phenotypes defined?

Is the rationale for creating the dataset(s) clearly described?
No

Are the protocols appropriate and is the work technically sound?
Yes

Are sufficient details of methods and materials provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Affective disorders, Twin cohorts, and biomarkers.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.