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Generalized anxiety disorder and health service use: findings from a large, population study

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Generalized anxiety disorder and health service use: findings from a large, population study

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3 31 **ABSTRACT**
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6 34 **OBJECTIVE**

7 35 Generalized anxiety disorder is the most common anxiety disorder in the general
8 36 population, and has been associated with high economic and human burden. However, it
9 37 has been neglected in the health services literature, with the exception of some studies
10 38 showing that it contributes to higher use of primary care services. The objective of this
11 39 study will be to assess whether generalized anxiety disorder leads to hospital admissions
12 40 using data from the European Prospective Investigation of Cancer-Norfolk.
13 41

14 42 **DESIGN**

15 43 Large, population study.
16 44

17 45 **SETTING**

18 46 UK population-based cohort.
19 47

20 48 **PARTICIPANTS**

21 49 30,445 people over the age of 40 were recruited through general practice registers in
22 50 England. Of these, 21,000 completed a structured health and lifestyle questionnaire used to
23 51 assess generalised anxiety disorder. Anxiety was examined in 1996-2000, and health service
24 52 use was captured between 1999/00 and 2009 through record linkage with large,
25 53 administrative health databases. 18,076 participants had complete data on covariates.
26 54

27 55 **MAIN OUTCOME MEASURE**

28 56 Past-year generalised anxiety disorder defined according to the Diagnostic and Statistical
29 57 Manual of Mental Disorders, fourth edition.
30 58

31 59 **RESULTS**

32 60 In this study, 2.2% (397/18,076) respondents had generalised anxiety disorder. Anxiety was
33 61 not independently associated with hospital admissions (IRR=1.01, 95% CI: 0.87, 1.16) over
34 62 nine years. However, those who developed anxiety before 30 years of age were at high risk
35 63 for hospital service use (IRR=1.24, 95% CI: 1.02, 1.50).
36 64

37 65 **CONCLUSION**

38 66 People with an earlier age of onset for generalized anxiety disorder had a higher risk for
39 67 hospital admissions over 9 years between 1999/00 and 2009 in the European Prospective
40 68 Investigation of Cancer-Norfolk study. Altogether, our findings show that anxiety that
41 69 developed early in life may be of a more severe form, and is associated with high health
42 70 service use rates. People with early-onset anxiety might be in poorer health than others;
43 71 clinicians should thus consider taking psychiatric histories of patients presenting with
44 72 anxiety complaints.
45 73

46 74 Key words: Anxiety, anxiety disorders, health services
47 75

76 **ARTICLE SUMMARY**77 **Strengths and limitations of this study**

- 78 • We used a large, population-based sample of middle- and older-aged adults and
79 adjusted for a range of important confounders, such as, sociodemographic factors
80 and medical history.
81
- 82 • We used a structured, self-reported questionnaire to assess presence of past-year
83 GAD, and participants were followed for 9 years.
84
- 85 • We examined health services through record linkage with large, administrative
86 health databases.
87
- 88 • Those who participated in this study were somewhat less deprived and healthier
89 than individuals living in other parts of England; therefore, our results may not
90 generalize to people living in extremely deprived circumstances.
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INTRODUCTION

93
94
95 Anxiety disorders[1] are the most common class of psychiatric disorders in the general
96 population. The Global Burden of Disease study[2] estimated that anxiety disorders
97 contribute to 26.8 million disability adjusted life years, and their annual direct cost is \$42.3
98 billion[3]. Generalized anxiety disorder (GAD) is a prevalent and disabling condition in
99 adults, and can lead to serious impairment in social and occupational functioning.[4] It is
100 associated with poor quality of life, impaired functioning and risk of suicide.[5-8] Across the
101 anxiety disorders, GAD has been found to be the most debilitating.[5, 9] Although there is
102 effective treatment for GAD, only a third of those affected receive any treatment.[8] This is
103 because anxiety disorders are frequently under-recognized and mismanaged by clinicians in
104 primary care, which is often the first point of contact for those with mental health problems.

105
106 Previous literature has suggested that patients with mental health problems tend to present
107 to their physician with physical rather than psychiatric symptoms, which leads to the
108 administration of extensive and costly medical tests in the search for a physical cause. This
109 implies that the problem has no physical basis (it is purely psychiatric in nature), and that
110 the patient, failing to recognize this, continues frequenting the general medical setting until
111 the underlying problem has been resolved.[9] Studies reiterate that effective treatment for
112 anxiety exists, but because physicians fail to recognize the origin of the patient's complaints
113 as psychiatric rather than physical, patients are not given the anxiolytic medication or
114 psychotherapy needed, hindering their recovery. However, it might be that anxiety
115 represents more than just worry-related symptoms that cannot be simply resolved through
116 psychological therapies or psychotropic medication. Anxiety disorders could be masking
117 underlying poor health or could be an early warning signal for future health problems that
118 are not yet detectable by standard medical tests.

119
120 Anxiety has been linked to hypothalamic-pituitary-adrenal (HPA)-axis dysregulation,
121 inflammation, and the release of pro-inflammatory cytokines, and this can lead to poor
122 health.[9] A recent study of hospitalized patients[10] also showed that people with anxiety
123 disorders had more physical comorbidities, including cardiovascular diseases and their risk
124 factors, compared to people without anxiety disorders.

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3 125 Early or late-onset forms of anxiety disorders should be also considered. A study[11] of over
4 126 one million Swedish men followed for over 20 years showed that early-onset forms of
5 127 mental disorders in particular led to increased risk of incident CHD. Therefore, identifying
6 128 clinical aspects, such as, individual anxiety disorders, early or late onset forms of the
7 129 disorder, and episode chronicity and frequency, can lead to better clinical management and
8 130 more accurate prediction of future disability and health service use.[12]
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15 132 The evidence base on health service use and anxiety is small and limited, and most of the
16 133 recent studies have focussed on post-traumatic stress disorder (PTSD) in war veterans.[13,
17 134 14] Most studies are based on clinical populations, cross-sectional designs, small samples,
18 135 short follow-up periods (usually one year), do not adequately control for confounders, and
19 136 use self-report to assess frequency or other measures of hospitalization patterns in the
20 137 clinical setting.
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28 138
29 139 Generalized anxiety disorder (GAD) is one of the most common anxiety disorders in the
30 140 general population[15] and the primary care setting[16], and has been associated with high
31 141 economic and human burden. However, it has been neglected in the health services
32 142 literature, with the exception of some studies showing GAD to contribute to higher use of
33 143 primary care services in primary care samples.[17-20] Whether GAD leads to hospital
34 144 admissions is unknown.
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40 145
41 146 The objective of this study will be to assess the association between generalized anxiety
42 147 disorder (GAD) and hospital service use in a longitudinal, population cohort of over 18,000
43 148 British individuals followed for 10 years. The aim is also to determine whether early or late
44 149 onset forms of the disorder, episode frequency and chronicity contribute to higher rates of
45 150 hospital services.
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METHODS

Study population

The study population was drawn from the European Prospective Investigation of Cancer-Norfolk longitudinal, cohort study, described in detail elsewhere.[21, 22] Briefly, a total of 30,445 participants over the age of 40 living in Norwich and the surrounding towns and rural areas were recruited between 1993 and 1997 using general practice registers. At baseline, they completed a health questionnaire capturing sociodemographics and medical history, and underwent a health check that gathered information on medication use. During follow-up, between 1993 and 1999/2000, participants completed self-reported postal questionnaires provided they: 1) were still alive, 2) did not ask to be removed from the study's mailing list, and 3) had a valid mailing address. Between 1996 and 1999/2000, respondents completed a Health and Life Experiences Questionnaire (HLEQ) used to capture information on psychiatric disorders, other psychosocial factors, and risk behaviours. Record linkage with administrative health databases using a unique identifier was used to determine hospitalization admissions data until 2009.

All participants recruited through general-practice registers and who completed a baseline health questionnaire were eligible to be included in our study; those who completed a psychosocial questionnaire during follow-up were eligible to be included in our analysis.

Assessment of generalized anxiety disorder (GAD)

The HLEQ was used to derive a measure of GAD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition. The HLEQ captured the onset and offset timings of episodes of past-year GAD.[23] Past-year GAD consisted of at least one episode that had offset within 12 months of administration of the HLEQ. DSM-IV GAD was diagnosed if participants reported having uncontrollable, excessive worry for six months or longer on most days than not that resulted in disability or impairment. In addition, at least three of the following symptoms needed to have been present: restlessness, irritability, muscle

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3 184 tension, fatigue, trouble concentrating because of worry, mind going blank, trouble falling
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5 185 asleep, trouble staying asleep, and feeling keyed up or on edge.
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8 187 **Assessment of covariates (potential confounders)**
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10 188
11 189 Potential confounders (based on the literature) included sociodemographics (age, sex,
12 190 education, marital status, social class, employment), prevalent physical diseases, MDD,
13 191 psychotropic medication use (antihypnotics and antidepressants), and risk behaviours
14 192 (alcohol use, smoking, physical activity). The final categorization of the variables took cell
15 193 size into account and was also done in accordance with previous literature.[23, 24-29] Age
16 194 was first assessed as a categorical variable, and subsequently divided into 10-year bands.
17 195 Sex was categorized into male vs. female; marital status was categorized into: married,
18 196 single (or never married), and others (widowed, divorced, separated); educational
19 197 attainment into high (vocational or formal qualifications at the A- or O-level or degree-level
20 198 qualifications) vs. low (no formal qualifications). Social class was derived using the
21 199 Computer-Assisted Standard Occupational Coding[29] and categorized as follows: I
22 200 (professionals), II (managerial and technical occupations), III non-manual and III manual
23 201 (skilled workers), IV (partly skilled workers), and V (unskilled manual workers). To assign
24 202 social class to men and women, the male partner's current or past occupation was used. If
25 203 this information was not available, the female partner's occupation was used. If the social
26 204 class from either partner was unavailable, then it was coded as missing. The final
27 205 categorization of social class included manual: skilled manual, partly skilled, and unskilled;
28 206 and non-manual: professionals, managerial and technical, and skilled non-manual. Marital
29 207 status was categorized into three groups: married, single (or never married), and others
30 208 (widowed, divorced, separated). Employment was divided into yes vs. no. Behaviour risk
31 209 factor measures included alcohol intake (units of alcohol/week), smoking status (current,
32 210 former, non-smoker), and physical activity (inactive, moderately inactive, moderately active,
33 211 active). Use of medications included hypnotic drug use (yes/no) and antidepressant drug
34 212 use (yes/no). Presence of past-year DSM-IV major depressive disorder (MDD) (yes/no) was
35 213 also assessed.[30]
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3 215 Individual-level health status was assessed through the construction of a variable capturing
4 216 major prevalent physical diseases associated with anxiety.[31] This was based on HLQ
5 217 questions asking participants: “Has the doctor ever told you that you have any of the
6 218 following?”, followed by a list of options, such as stroke, myocardial infarction, and cancer.
7
8 219 To determine disability levels, we used the physical component summary score (PCS) of the
9 220 Medical Outcomes Study 36-Item Short Form (SF-36), a widely-used, validated self-
10 221 assessment tool. A score of 100 represents no disability and 0 represents a high level of
11 222 disability.[32] PCS scores were dichotomized above and below the median.
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19 224 All of these individual-level variables were regarded as potential confounders and selected
20 225 based on the literature and their association with anxiety and deprivation.[33, 34]
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24 227 **Hospital service use**

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28 229 All analyses are based on non-psychiatric hospitalizations. Primary care service use was not
29 230 captured in this study.
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33 232 Frequency of hospitalization between 1999/00 and 2009 was determined using
34 233 administrative health databases maintained by the National Health Service. The East
35 234 Norfolk Primary Health Care trust databases were used, and these are updated on an
36 235 ongoing basis and provide information on clinical and administrative data from participating
37 236 facilities, such as, hospitals.
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43 238 England is under a publicly-funded health care system (the National Health Service), free at
44 239 the point of delivery; therefore, we expect factors, such as access to health insurance or
45 240 personal income, to have minimal impact on the care that is obtained by study participants.
46 241 The databases used in this study are maintained by the National Health Service, which is
47 242 likely to capture most hospital admissions from the population, as private sector provision is
48 243 minimal. This means that admissions data in our study can be considered complete for the
49 244 ascertainment of hospital/health service use, and the likelihood of bias minimal. To access
50 245 hospital services in the UK, a referral is needed from the primary care practitioner, who acts
51 246 as a gate-keeper to secondary care.
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3 247 The East Norfolk Primary Health Care databases were linked to the EPIC-Norfolk cohort
4 248 using participants' unique National Health Service number, which allows complete record
5 249 linkage across settings and calendar time.
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10 251 Vital status for participants was determined through record linkage with the United
11 252 Kingdom Office of National Statistics. Vital status was available for all participants. This
12 253 allowed us to exclude those who died before their health service use was ascertained.
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15 254

16 255 **Statistical Analysis**

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19 257 First, demographics, social class, medical and psychiatric co-morbidities, risk behaviours,
20 258 and medication use were compared by GAD status. Second, frequency of hospitalization
21 259 was compared by GAD status.
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27 261 Since the number of hospital admissions was skewed and the variance was much larger than
28 262 the mean, zero-inflated negative binomial regression was used for frequency of hospital
29 263 utilization (number of hospital admissions). The log-likelihood test showed that this model
30 264 was superior to Poisson regression. Three models were fitted for hospital admissions with
31 265 progressive adjustment of covariates: model A adjusted for sociodemographics (age, sex,
32 266 education, social class, employment), physical comorbidities and disability; model B further
33 267 accounted for past-year MDD (assessed at the same questionnaire point as past-year GAD);
34 268 and model C further controlled for antihypnotic and antidepressant medications, physical
35 269 activity, alcohol, and smoking.
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45 271 Finally, we determined whether the risk for hospitalization was higher among those with: 1)
46 272 3 or more episodes of lifetime GAD (versus fewer than 3 episodes), 2) age of onset at 30
47 273 years or younger (versus over 30 years), and 3) episodes that lasted on average 6 months or
48 274 more (versus fewer than 6 months). Two-sided statistical tests were conducted and a p-
49 275 value of <0.05 was used for statistical significance. Analyses were implemented in SAS,
50 276 version 9.3.
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3 278 To arrive at the study size, we went through the following steps: of the 30,445 who
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5 279 completed the baseline HLQ, we retained those participants who completed the HLEQ
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7 280 (20,921), and of these, we kept those people with complete data on all covariates (18,076).
8
9 281 (Figure 1)

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12 283 **Patient involvement**

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16 285 There were no patients involved in the development of the research question and outcome
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18 286 measures, the design of the study, or the recruitment to and conduct of the study.

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RESULTS

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290 Of the 30,445 people recruited at baseline, 20,921 participants completed the HLEQ; we had
291 479 missing observations for past-year GAD, 700 for past-year MDD, 1386 for SF-36, and the
292 rest of the missing observations (280) were generated from the other covariates. The final
293 sample included a total of 18,076 participants. Participants were assessed between
294 1999/00 and 2009 (followed for 9 years) (Figure 1).

295

296 In 1996-2000, GAD was present in 397 out of 18,076 (2.2%) people. Table 1 shows the
297 baseline characteristics of participants by GAD status.

298

299 **Table 1 Percentage and number of people with past-year GAD reported in 1996-2000**
 300 **according to sociodemographic factors, health status, and behaviour risk factors for the**
 301 **EPIC-Norfolk cohort (n=18,076)**
 302

Characteristic	Number with characteristic	Percentage and number with past-year GAD
Socio-demographics		
Age (years)		
<50	2369	3.4 (81)
50-60	6242	2.9 (180)
60-70	5782	1.6 (94)
70+	3683	1.1 (42)
Sex		
Women	10037	2.5 (252)
Men	8039	1.8 (145)
Education[‡]		
Low	6189	2.0 (122)
High	11887	2.3 (275)
Marital status		
Single	690	3.6 (25)
Married	14640	2.0 (287)
Other*	2746	3.1 (85)
Social class		
Manual	6910	2.0 (139)
Non-manual	11166	2.3 (258)
Employment		
Yes	7742	2.0 (156)
No	10334	2.3 (241)
Health status		
Physical comorbidities⁺		
Yes	9237	2.7 (253)
No	8839	1.6 (144)
Disability level		
High [¶]	8989	3.0 (270)
Low	9087	1.4 (127)
Psychiatric comorbidity		
Past-year MDD		
Yes	941	21.6 (203)
No	17135	1.1 (194)
Lifestyle		
Physical activity		
Active [‡]	12882	2.1 (272)
Inactive	5194	2.4 (125)
Smoking status		
Current smoker	1907	4.8 (92)
Former smoker	7510	1.9 (141)
Never smoker	8659	1.9 (164)
Alcohol intake		
High [¶]	9242	2.0 (183)

Low	8834	2.4 (214)	303
Medication			
Antidepressant use			
Yes	632	15.4 (97)	306
No	17444	1.7 (300)	307
Antihypnotic use			
Yes	2799	2.4 (68)	308
No	15277	2.2 (329)	309

310 + Prevalent physical disease: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart
 311 attack, cancer, diabetes, thyroid conditions, arthritis

312 ‡ Moderately inactive, moderately active, active

313 † High education: O-level, A-level, degree; low education: refers to no education

314 * Other: divorced, separated, widowed

315 ¶ Below the median PCS value of 50.6

316 ^a 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

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3 317 Those with GAD were more likely to be younger, women, inactive, current smokers, low
4 318 alcohol consumers, of higher educational attainment, single, non-manual social class,
5 319 without employment, with physical comorbidities, high levels of disability, MDD, and to take
6 320 antidepressant and antihypnotic medications. Table 2 summarizes the means and standard
7 321 deviations of the number of hospital admissions by participant characteristics.
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323 **Table 2: Hospital admissions (mean, SD) by participant characteristics in 18,076 British**
 324 **people between 1999/00 and 2009**
 325

Characteristic	Total number with characteristic	Number of admissions Mean (SD)
Past-year GAD		
Yes	397	4.1 (6.3)
No	17679	3.4 (13.0)
Socio-demographics		
Age (years)		
<50	2369	1.9 (9.8)
50-60	6242	3.0 (16.4)
60-70	5782	3.8 (11.1)
70+	3683	4.6 (9.6)
Sex		
Women	10037	3.1 (14.0)
Men	8039	3.9 (11.3)
Education[†]		
Low	6189	4.1 (17.0)
High	11887	3.1 (10.0)
Marital status		
Single	690	3.0 (8.9)
Married	14640	3.4 (10.9)
Other*	2746	4.0 (20.9)
Social class		
Manual	6910	4.0 (18.2)
Non-manual	11166	3.1 (7.9)
Employment		
Yes	7742	2.5 (9.1)
No	10334	4.1 (15.0)
Health status		
Physical comorbidities[‡]		
Yes	9237	3.9 (10.4)
No	8839	3.0 (15.0)
Disability level		
High [¶]	8989	4.4 (16.4)
Low	9087	2.5 (7.8)
Psychiatric comorbidity		
Past-year MDD		
Yes	941	4.6 (13.6)
No	17135	3.4 (12.8)
Lifestyle		
Physical activity		
Active [‡]	12882	3.2 (13.3)
Inactive	5194	4.1 (11.6)
Smoking status		
Current smoker	1907	4.6 (26.7)

Former smoker	7510	3.8 (11.4)	326
Never smoker	8659	2.9 (8.9)	
Alcohol intake			
High ^a	9242	3.2 (13.3)	
Low	8834	3.7 (12.4)	
Medication			
Antidepressant use			
Yes	632	5.2 (19.8)	
No	17444	3.4 (12.5)	
Antihypnotic use			
Yes	2799	5.2 (23.6)	
No	15277	3.1 (9.6)	

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* Prevalent physical disease: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

‡ Moderately inactive, moderately active, active

‡ High education: O-level, A-level, degree; low education: refers to no education

* Other: divorced, separated, widowed

[¶] Below the median PCS value of 50.6

^a 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

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3 336 Participants with GAD had a higher frequency of hospitalization compared to those without
4 337 GAD. Some of the findings show that frequency of hospitalization was markedly higher
5 338 among older age groups, men, those with low educational attainment, unemployed
6 339 participants, those with high levels of disability, past-year MDD and individuals taking
7 340 medication.
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12 342 Table 3 shows the unadjusted and adjusted incidence rate ratios of hospital admissions by
13 343 GAD status.
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345 **Table 3: Associations between past-year GAD reported in 1996-2000 and hospital**
 346 **admissions in 1999/00-2009 in 18,076 British people over the age of 40**
 347

IRR and 95% CI				
Characteristic	Crude IRR	A ¹	B ²	C ³
Past-year GAD				
Yes	1.19 (1.03, 1.37)	1.26 (1.10, 1.45)	1.11 (0.96, 1.28)	1.01 (0.87, 1.16)
No	1.00	1.00	1.00	1.00
Socio-demographics				
Age				
Per 10 years	1.36 (1.33, 1.39)	1.19 (1.16, 1.23)	1.20 (1.17, 1.24)	1.20 (1.16, 1.24)
Sex				
Women	0.80 (0.77, 0.83)	0.76 (0.73, 0.79)	0.76 (0.72, 0.79)	0.77 (0.73, 0.80)
Men	1.00	1.00	1.00	1.00
Education[‡]				
Low	1.30 (1.25, 1.36)	1.13 (1.08, 1.18)	1.14 (1.09, 1.19)	1.12 (1.07, 1.17)
High	1.00	1.00	1.00	1.00
Marital status				
Single	0.88 (0.79, 0.99)	0.85 (0.77, 0.95)	0.85 (0.76, 0.94)	0.84 (0.75, 0.93)
Married	1.00	1.00	1.00	1.00
Other*	1.21 (1.14, 1.28)	1.17 (1.10, 1.24)	1.14 (1.07, 1.20)	1.08 (1.02, 1.14)
Social class				
Manual	1.29 (1.24, 1.35)	1.25 (1.19, 1.30)	1.25 (1.19, 1.30)	1.19 (1.14, 1.25)
Non-manual	1.00	1.00	1.00	1.00
Employment				
Yes	1.00	1.00	1.00	1.00
No	1.63 (1.57, 1.70)	1.18 (1.12, 1.25)	1.17 (1.11, 1.24)	1.13 (1.08, 1.20)
Health status				
Physical comorbidities⁺				
Yes	1.32 (1.27, 1.38)	1.18 (1.13, 1.23)	1.17 (1.13, 1.23)	1.17 (1.12, 1.22)
No	1.00	1.00	1.00	1.00
Disability level				
High [¶]	1.78 (1.71, 1.85)	1.51 (1.45, 1.58)	1.51 (1.44, 1.57)	1.43 (1.37, 1.50)
Low	1.00	1.00	1.00	1.00
Psychiatric comorbidity				
Past-year MDD				
Yes	1.35 (1.23, 1.48)		1.34 (1.22, 1.48)	1.29 (1.18, 1.42)
No	1.00		1.00	1.00
Medications				
Antihypnotic use				
Yes	1.67 (1.58, 1.77)			1.28 (1.21, 1.35)
No	1.00			1.00
Antidepressant use				
Yes	1.54 (1.38, 1.72)			1.27 (1.14, 1.42)

No	1.00	1.00
Lifestyle		
Physical activity		
Active [‡]	1.00	1.00
Inactive	1.27 (1.21, 1.33)	1.04 (0.99, 1.08)
Smoking status		
Current smoker	1.59 (1.48, 1.71)	1.47 (1.37, 1.57)
Former smoker	1.32 (1.26, 1.38)	1.12 (1.07, 1.17)
Never smoker	1.00	1.00
Alcohol intake		
High [¶]	0.88 (0.85, 0.92)	0.92 (0.88, 0.96)
Low	1.00	1.00

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349 ¹ Model A: adjusted for age, sex, education, marital status, social class, employment, physical comorbidities350 ² Model B: adjusted for sociodemographics, physical comorbidities, MDD351 ³ Model C: adjusted for sociodemographics, physical comorbidities, MDD, antihypnotic use, antidepressant
352 use, physical activity, smoking, alcohol353 ^{*} Physical co-morbidities: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart
354 attack, cancer, diabetes, thyroid conditions, arthritis355 [‡] Moderately inactive, moderately active, active356 [‡] High education: O-level, A-level, degree; low education: refers to no education357 ^{*} Other: divorced, separated, widowed358 [¶] Below the median PCS value of 50.6359 [¶] 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

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3 360 After adjustment for sociodemographic variables, physical comorbidities, and disability, GAD
4 361 was associated with a 26% higher incidence rate of hospitalization (IRR=1.26, 95% CI: 1.10,
5 362 1.45). The incidence rate ratio was somewhat attenuated and became statistically non-
6 363 significant after further adjustment for MDD (IRR=1.11, 95% CI 0.96, 1.28). The effect
7 364 estimate approached the null after further adjustment for medication use and lifestyle
8 365 factors (IRR=1.01, 95% CI: 0.87, 1.16).
9 366

10 367 Next, we assessed whether risk for hospital admissions varied by frequency of lifetime
11 368 episodes, age of onset, and episode chronicity. People who developed GAD before 30 years
12 369 of age were 24% more likely to be admitted to the hospital than those who developed it
13 370 later in life (IRR=1.24, 95% CI: 1.02, 1.50). People with more than 3 lifetime episodes also
14 371 had a higher risk of hospitalizations, but the association did not reach statistical significance
15 372 (IRR=1.15, 95% CI: 0.98, 1.35). Those whose episodes lasted, on average, 6 months or
16 373 longer did not have an increased risk for admissions compared to those with shorter
17 374 episodes (IRR=1.09, 95% CI: 0.87, 1.36).
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DISCUSSION

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377 This is the first study to assess the association between generalized anxiety disorder (GAD)
378 and hospital service use in a population-based cohort. This longitudinal study showed that
379 having an episode of GAD in the past year was not independently associated with hospital
380 admissions during the subsequent ten years. However, those who developed GAD at an
381 early age (before 30) were at a significantly increased risk for being admitted to hospital
382 than those with a later onset.

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384 People with past-year GAD were more likely to have medical comorbidities; therefore, the
385 association with hospital service use was partially driven by worse physical health in those
386 with anxiety. Psychiatric co-morbidity also led to attenuation of the effect estimate for
387 those who experienced an episode of GAD in the past year. Major depressive disorder
388 (MDD) is highly comorbid with GAD, and when it was introduced in the models, it explained
389 away any remaining associations with hospital service utilization in the primary analyses.

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391 When the course of GAD was considered, the risk for hospitalization was found to be much
392 higher in those who developed anxiety at an early age, after adjusting for physical diseases,
393 psychiatric comorbidity, and behaviour risk factors.

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Strengths and limitations

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397 There are several strengths associated with our study. We had a large, population-based
398 sample of middle- and older-aged adults and adequately adjusted for a range of possible
399 confounders. We used a structured questionnaire to assess past-year GAD according to
400 DSM-IV criteria, used large administrative health databases to examine hospital service use
401 (avoiding the self-reporting bias found in questionnaire studies), and participants were
402 followed for a long time. We had a large list of self-reported physician diagnoses of chronic
403 diseases that we used to ascertain medical histories. Despite this, the residual effect of
404 diseases not captured by our study, but that are associated with GAD may be present. Past
405 illness may have been underreported, which may have introduced measurement error and
406 further attenuated effect estimates towards the null. A negligible proportion of participants

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3 407 may have obtained care at private facilities, which might have led to non-differential
4 408 misclassification. The databases used in this study also did not capture admissions to
5 409 hospitals outside the UK. However, migration in the EPIC-Norfolk cohort is minimal and
6 410 does not present a problem.
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11 412 We may have overadjusted our models with the inclusion of self-evaluated impairment, as
12 413 this may be part of the expression of psychiatric illness. This can lead to attenuation of
13 414 effect estimates. If participants chose not to answer certain questions in the HLEQ, this
14 415 contributed to missing data; however, to avoid biasing the findings, we retained participants
15 416 for whom we had complete data on all covariates. Non-participation in our study also may
16 417 have led to non-differential misclassification and further attenuation of effect estimates.
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24 419 Another limitation is that we did not have data on primary care service use. Merging
25 420 population cohorts, such as ours, with primary care service administrative databases and
26 421 hospitalization databases would have provided a more complete picture of the burden of
27 422 GAD on the health care system.
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33 424 Participants were required to complete detailed dietary and lifestyle questionnaires and
34 425 undergo periodic health assessments. Because those who participated in EPIC-Norfolk were
35 426 more affluent and healthier than individuals living in other parts of England, our results may
36 427 not generalize to people living in extremely deprived areas.
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41 429 **Comparison with other studies**

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45 431 Most of the studies assessing the link between psychiatric disorders and non-psychiatric
46 432 health service utilization have focused on depression and, to a lesser extent, panic disorder
47 433 and PTSD, while other anxiety disorders have been significantly underresearched. Most of
48 434 the studies on depression have shown an association with health service use in both clinical
49 435 and community samples.[35] There are substantially fewer studies on anxiety, and a
50 436 number of these have shown positive associations with health service use. A US study[36]
51 437 that recruited patients from an outpatient clinic showed that anxiety disorders were linked
52 438 to higher utilization of primary care services compared to depressive or addictive disorders.
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3 439 Patients, however, were recruited from an outpatient clinic located in a predominantly rural
4 440 area, which might have affected generalizability. Another study showed anxiety disorders
5 441 to be associated with a higher number of consultations in general medical, emergency and
6 442 specialty settings, such as cardiology and dermatology.[37] In this study, people were
7 443 sampled from an anxiety clinic, thereby leading to possible selection bias. PTSD has also
8 444 been associated with health service use, such as more ordered lab tests and medications
9 445 prescribed compared to those without this disorder, but much of the literature on this[14,
10 446 38] has been based on highly-select samples that have limited generalizability. Two of the
11 447 more recent studies on GAD showed it to be associated with health care use. One Canadian
12 448 study[19] suggested a higher rate of medical visits to primary care practitioners in those
13 449 with GAD, while a US study[17] also found a higher frequency of specialty medical care visits
14 450 in affected individuals. Both of these studies recruited clinical samples, with the potential
15 451 for self-selection bias. None of these studies assessed whether the severity of anxiety
16 452 contributes to even higher health service use rates (early onset forms of the disorder are
17 453 typically the most severe, hardest to treat and with the poorest prognosis [9]).
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455 **Mechanisms**

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457 A more severe course of GAD, marked by early age of onset, can lead to higher rates of
458 health services because of unhealthy behaviours, such as smoking and alcohol. When we
459 controlled for these covariates, the associations with hospitalizations remained significant.
460 It could also be that anxiety is associated with poorer underlying health, which leads to
461 higher health service use rates. Although we controlled for several chronic diseases, we
462 might have missed some conditions that are associated with GAD and hospitalizations. A
463 third explanation for higher health service use in those with anxiety could relate to
464 inflammatory pathways. If clinically apparent signs of disease have not yet developed in
465 those with anxiety or are at an early, undetectable stage, it will not be possible to measure
466 these factors and adjust for them in analyses.

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3 468 **Implications**
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6 470 Generalized anxiety disorder is a debilitating and impairing condition.[9] The evidence base
7 471 on its association with health services is small and confined to clinical settings with the
8 472 potential for self-selection bias. Our study overcomes many limitations of previous studies,
9 473 and shows, for the first time that early age of onset of generalized anxiety disorder is
10 474 associated with increased use of hospital services in adults, after controlling for a range of
11 475 important confounders.
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18 477 Population-based research on anxiety is lacking, and thus far, no studies have assessed the
19 478 association between GAD and non-psychiatric hospitalization. Clinicians should consider
20 479 that it is not just the diagnosis of the disorder at one point in time that is predictive of
21 480 deleterious health outcomes; its long-term course is also important. GAD has a waxing and
22 481 waning course throughout a patient's life, and many of those affected experience relapse
23 482 after psychiatric treatment. Furthermore, early-onset forms of the disorder have been
24 483 shown to be more severe, and are the most difficult to treat and have a poor prognosis.[9]
25 484 As such, examining the course of the disorder and determining the age of onset makes
26 485 theoretical sense and has clinical implications. Taking a patient's medical history when the
27 486 presenting complaints are related to anxiety can differentiate those with milder forms
28 487 (knowing this can reduce unnecessary follow-up investigations) from those with more
29 488 severe cases that would benefit from medical follow-up. Assessing the presence of GAD
30 489 using DSM-IV criteria is time-consuming in a busy, clinical practice; hence, future studies
31 490 should replicate our study using brief, validated screening tools. Our findings are also
32 491 important for policy-makers. Large numbers of people are affected by anxiety and develop
33 492 GAD early in life (this group then shows a disproportionate consumption of health
34 493 services)[9], therefore, policy-makers should consider rolling out more widespread anxiety
35 494 prevention and screening programmes.
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52 496 We would like to make some recommendations for future research. Younger people are
53 497 most affected by anxiety disorders[31], therefore, future studies should assess these
54 498 associations in younger cohorts. Second, clinical studies have shown depression to be highly
55 499 co-morbid with GAD[16], hence, the impact of comorbidity on the health care system
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3 500 should also be examined. Third, previous studies suggest, that across the anxiety disorders,
4 501 GAD is the most likely to lead to the development and maintenance of chronic
5 502 conditions.[9] To this end, the mediating effect of chronic conditions in relation to anxiety
6 503 should be examined. Finally, future research should merge a population-based cohort with
7 504 primary and secondary care administrative health databases to provide a more complete
8 505 picture of the burden of anxiety on the health care system.
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507 **Conclusion**

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19 509 People with an earlier age of onset for generalized anxiety disorder (GAD) had a higher risk
20 510 for hospital admissions over 10 years between 1996-1999 and 2009 in the European
21 511 Prospective Investigation of Cancer in Norfolk study. Altogether, our findings show that a
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23 512 more severe course of anxiety is associated with high health service use rates.
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23 529 all aspects of the work, gave final approval of the version to be published, and made
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27 533 of the data analysis. OR acts as guarantor of the study.

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30 535 Transparency declaration: OR affirms that the manuscript is an honest, accurate, and
31 536 transparent account of the study being reported; that no important aspects of the study
32 537 have been omitted; and that any discrepancies from the study as planned have been
33 538 explained.

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37 541 the design and conduct of the study; collection, management, analysis, and interpretation of
38 542 the data; and preparation, review, or approval of the manuscript.

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3 544 Ethical approval: The study has ethics committee approval from Norfolk Ethics Committee
4 545 (Rec Ref: 98CN01) and all participants gave informed consent.

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8 547 Data sharing: No additional data available. Original dataset requests should be sent to the
9 548 corresponding author. Please contact O Remes at or260@medschl.cam.ac.uk for questions
10 549 about the statistical code.

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3 688 **Figure 1 – Flowchart of EPIC-Norfolk cohort**
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5 689 This is a flowchart showing the number of participants at each study stage: the number
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7 690 approached to participate in the EPIC-Norfolk study, the number enrolled at baseline, and
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9 691 with complete data on all covariates. The EPIC-Norfolk study consists of middle-aged and
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11 692 older British people.
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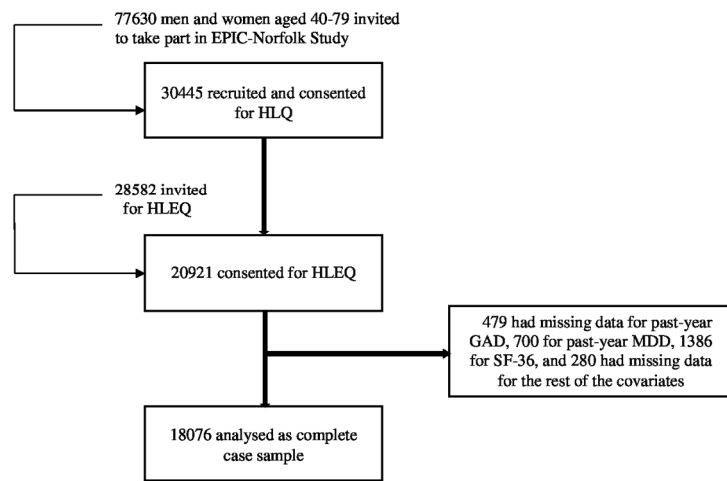


Figure 1: Flowchart of EPIC-Norfolk cohort

215x279mm (200 x 200 DPI)

Please see the article line numbers (column on the right) and the explanations provided.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Line numbers within the article
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	9, 40, 43 35-68
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	95-144
Objectives	3	State specific objectives, including any prespecified hypotheses	146-150
Methods			
Study design	4	Present key elements of study design early in the paper	157-158
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	158-169
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	158-160, 162-165
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	175-252
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is	There were two variables of interest in this study: generalized anxiety disorder and hospital admissions

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more than one group

(175-185, 226-252). The others are potential confounders – in the methods I list them all, indicate how they were assessed and mention that they were collected through the baseline, self-reported postal HLQ questionnaire as well as the HLEQ.

Bias	9	Describe any efforts to address potential sources of bias	278 (complete case analysis)
Study size	10	Explain how the study size was arrived at	276-278
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	In the methods, I mention how the variables were derived based on the raw data provided by participants in the questionnaires. Confounders: 193-212; Generalized anxiety disorder: 180-185; Information on how health service use data was handled in analyses: 260-262
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	254-278
		(b) Describe any methods used to examine subgroups and interactions	We did not examine any subgroups or interactions.
		(c) Explain how missing data were addressed	We indicated that this was a complete-case analysis.
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	Loss to follow-up was not a problem in this study. We were able to track down all participants using various means, unless they expressed that they wished to be removed from the mailing list. We elaborate on this in the manuscript.
		(e) Describe any sensitivity analyses	There were no sensitivity analyses.

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	287-291
		(b) Give reasons for non-participation at each stage	We do not have the reasons for non-participation, because these data were not collected when the study was initiated in 1993.
		(c) Consider use of a flow diagram	Flow diagram included in submission.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	293-294, 296-312, 314-317; we provided characteristics for those with vs. without GAD, because we felt it was important to show the characteristics of the ‘exposed’ vs. ‘non-exposed’ group (see also Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	287-289
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	291
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	293
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 contains unadjusted and progressively adjusted estimates. We also discussed the findings within the text, and provide odds ratios and 95% confidence intervals. We included the confounders based on the literature – we mention this in the paper. As per strobe, we included this information in the methods section; and we omitted repeating this in the results section to reduce redundancy. However, if the editor would like us to repeat this information in the results, we are happy to do so.
		(b) Report category boundaries when continuous variables were categorized	The age cut-offs are provided. In regards to the

physical component summary of the SF-36, the methods section states that those below and above the median cut-point were compared. The results section (footnotes of the tables) indicates that 3 units of alcohol was the cut point used to differentiate those with ‘high’ versus ‘low’ alcohol intake.

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable.
Discussion			
Key results	18	Summarise key results with reference to study objectives	375-379, 388-390
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	400-424
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	465-490 and 505-508 (We also have a section comparing our study results to those of others: 426-450 as well as a section on potential mechanisms explaining our findings: 452-463)
Generalisability	21	Discuss the generalisability (external validity) of the study results	423-424
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	518-519

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Generalized anxiety disorder and non-psychiatric hospital admissions: findings from a large, population study

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Generalized anxiety disorder and non-psychiatric hospital admissions: findings from a large, population study

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Figures: 1; Tables: 4

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2
3 31 **ABSTRACT**
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6 34 **OBJECTIVE**

7 35 Generalized anxiety disorder (GAD) is the most common anxiety disorder in the general
8 36 population, and has been associated with high economic and human burden. However, it
9 37 has been neglected in the health services literature. The objective of this study will be to
10 38 assess whether GAD leads to non-psychiatric hospital admissions using data from the
11 39 European Prospective Investigation of Cancer-Norfolk. Other aims include determining
12 40 whether early or late onset forms of the disorder, episode chronicity and frequency, and
13 41 comorbidity with major depressive disorder (MDD) contribute to non-psychiatric hospital
14 42 admissions.
15 43

16 44 **DESIGN**

17 45 Large, population study.
18 46

19 47 **SETTING**

20 48 UK population-based cohort.
21 49

22 50 **PARTICIPANTS**

23 51 30,445 people over the age of 40 were recruited through general practice registers in
24 52 England. Of these, 20,919 completed a structured health and lifestyle questionnaire used to
25 53 assess GAD. Anxiety was examined in 1996-2000, and health service use was captured
26 54 between 1999/00 and 2009 through record linkage with large, administrative health
27 55 databases. 17,939 participants had complete data on covariates.
28 56

29 57 **MAIN OUTCOME MEASURE**

30 58 Past-year GAD defined according to the Diagnostic and Statistical Manual of Mental
31 59 Disorders, fourth edition.
32 60

33 61 **RESULTS**

34 62 In this study, 2.2% (393/17,939) respondents had GAD. Anxiety was not independently
35 63 associated with non-psychiatric hospital admissions (IRR=1.04, 95% CI: 0.90, 1.20) over nine
36 64 years. However, those who developed anxiety before 30 years of age seemed to be at
37 65 increased risk for hospital service use (IRR=1.16, 95% CI: 0.95, 1.41). Those whose anxiety
38 66 was comorbid with depression showed a statistically significant association with non-
39 67 psychiatric hospital admissions (IRR=1.23, 95% CI: 1.02, 1.49).
40 68

41 69 **CONCLUSION**

42 70 People with an earlier age of GAD onset and who had MDD comorbidity were at an
43 71 increased risk for hospital admissions. Clinicians should consider that it may not be the
44 72 diagnosis of the disorder at one point in time that is predictive of deleterious health
45 73 outcomes; rather its long-term course and different forms of the disorder might be of
46 74 greater importance.
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48 76 Key words: Anxiety, anxiety disorders, health services
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78 **ARTICLE SUMMARY**79 **Strengths and limitations of this study**

- 80 • We used a large, population-based sample of middle- and older-aged adults and
81 adjusted for a range of important confounders, such as, sociodemographic factors
82 and medical history.
83
- 84 • We used a structured, self-reported questionnaire to assess presence of past-year
85 GAD, and participants were followed for 9 years.
86
- 87 • We examined health services through record linkage with large, administrative
88 health databases.
89
- 90 • Those who participated in this study were somewhat less deprived and healthier
91 than individuals living in other parts of England; therefore, our results may not
92 generalize to people living in extremely deprived circumstances.
93
94

INTRODUCTION

95
96
97 Anxiety disorders[1] are the most common class of psychiatric disorders in the general
98 population. The Global Burden of Disease study[2] estimated that anxiety disorders
99 contribute to 26.8 million disability adjusted life years, and their annual direct cost is \$42.3
100 billion[3]. Generalized anxiety disorder (GAD) is characterized by excessive, pervasive
101 worry, and a number of additional symptoms, such as restlessness and muscle tension. It is
102 a prevalent and disabling condition in adults, and can lead to serious impairment in social
103 and occupational functioning.[4] GAD is associated with poor quality of life, impaired
104 functioning and risk of suicide.[5-8] Across the anxiety disorders, this condition has been
105 found to be the most debilitating.[5, 9] Although there is effective treatment for GAD, only
106 a third of those affected receive any treatment.[8] This is because anxiety disorders are
107 frequently under-recognized and mismanaged by clinicians in primary care, which is often
108 the first point of contact for those with mental health problems.[10]

109
110 Although detection of anxiety in clinical settings is poor[11, 12] and the presence of
111 undiagnosed mental health problems can contribute to further emotional distress in
112 patients down the line[12], it could be that disorders such as GAD represent more than just
113 psychological or worry-related symptoms. It may be that anxiety symptoms are masking
114 underlying poor physical health or could be an early warning signal for future health
115 problems that are not yet detectable by standard medical tests. Such problems cannot be
116 simply resolved through psychological therapies or psychotropic medication.

117
118 Anxiety has been linked to hypothalamic-pituitary-adrenal (HPA)-axis dysregulation and
119 inflammation, and this can lead to poor health.[9] A recent study of hospitalized
120 patients[13] also showed that people with anxiety disorders had more co-morbid physical
121 conditions, including cardiovascular diseases and their risk factors, compared to people
122 without anxiety disorders. Conversely, anxiety could also represent a response to
123 underlying medical illness, and physical illness can exacerbate anxiety; the possibility of a
124 bidirectional relationship between anxiety and physical health should not be excluded.[14,
125 15] Compelling evidence from prospective studies, however, has shown that anxiety can

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3 126 indeed increase the risk of serious chronic conditions, such as cancer[16] and coronary heart
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5 127 disease (CHD)[17].

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7 128 When investigating the links between mental disorders and health outcomes, early or late-
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9 129 onset forms of anxiety disorders, as well as psychiatric comorbidity should be also
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11 130 considered. A study[18] of over one million Swedish men followed for over 20 years
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13 131 showed that early-onset forms of mental disorders in particular led to increased risk of
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15 132 incident CHD. Anxiety disorders, such as, GAD are also frequently comorbid with major
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17 133 depressive disorder (MDD)[19], and psychiatric comorbidity has been associated with
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19 134 poorer quality of life, worse prognosis, and higher use of health services for mental health
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21 135 problems than pure forms of the disorder.[20, 21, 22] Therefore, identifying clinical aspects,
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23 136 such as, early or late onset forms of the condition, episode chronicity and frequency, and
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25 137 comorbidity with MDD can lead to better clinical management and more accurate
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27 138 prediction of future disability and health service use.[23]

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31 140 GAD is one of the most common anxiety disorders in the general population[24] and the
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33 141 primary care setting[25], and has been associated with high economic and human burden.
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35 142 However, it has been neglected in the health services literature, with the exception of some
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37 143 studies showing GAD to contribute to higher use of primary care services in primary care
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39 144 samples.[26-29] Clinical samples, however, have the potential for self-selection bias.
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41 145 Whether GAD leads to non-psychiatric hospital admissions is unknown.

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45 147 The objective of this study will be to assess the association between GAD and non-
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47 148 psychiatric hospital admissions in a longitudinal, population cohort of over 18,000 British
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49 149 individuals followed for 10 years. The aim is also to determine whether early or late onset
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51 150 forms of the disorder, episode frequency and chronicity, and comorbidity with MDD
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53 151 contribute to non-psychiatric hospital admissions.

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METHODS

Study population

The study population was drawn from the European Prospective Investigation of Cancer-Norfolk longitudinal, cohort study, described in detail elsewhere.[30, 31] Briefly, a total of 30,445 participants over the age of 40 living in Norwich and the surrounding towns and rural areas were recruited between 1993 and 1997 using general practice registers. At baseline, they completed a health questionnaire capturing sociodemographics and medical history. During follow-up, between 1993 and 1999/2000, participants completed self-reported postal questionnaires provided they: 1) were still alive, 2) did not ask to be removed from the study's mailing list, and 3) had a valid mailing address. Between 1996 and 1999/2000, respondents completed a Health and Life Experiences Questionnaire (HLEQ)[30] used to capture information on psychiatric disorders, other psychosocial factors, and risk behaviours. Record linkage with administrative health databases using a unique identifier was used to determine hospitalization admissions data until 2009.

All participants recruited through general-practice registers and who completed a baseline health questionnaire were eligible to be included in our study; those who completed a psychosocial questionnaire during follow-up were eligible to be included in our analysis.

Assessment of GAD

The HLEQ was used to derive a measure of GAD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition. The HLEQ captured the onset and offset timings of episodes of past-year GAD.[32] Past-year GAD consisted of at least one episode that had offset within 12 months of administration of the HLEQ. DSM-IV GAD was diagnosed if participants reported having uncontrollable, excessive worry for six months or longer on most days than not that resulted in disability or impairment. In addition, at least three of the following symptoms needed to have been present: restlessness, irritability, muscle tension, fatigue, trouble concentrating because of worry, mind going blank, trouble falling asleep, trouble staying asleep, and feeling keyed up or on edge.

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3 186 **Assessment of covariates**
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6 188 Potential confounders (based on the literature) included sociodemographics (age, sex,
7 189 education, marital status, social class, employment), prevalent physical diseases, disability,
8 190 MDD, and risk behaviours (alcohol use, smoking, physical activity). The final categorization
9 191 of the variables took cell size into account and was also done in accordance with previous
10 192 literature.[32, 33-38] Age was first assessed as a categorical variable, and subsequently
11 193 divided into 10-year bands. Sex was categorized into male vs. female; marital status was
12 194 categorized into: married, single (or never married), and others (widowed, divorced,
13 195 separated); educational attainment into high (vocational or formal qualifications at the A- or
14 196 O-level or degree-level qualifications) vs. low (no formal qualifications). Social class was
15 197 derived using the Computer-Assisted Standard Occupational Coding[38] and categorized as
16 198 follows: I (professionals), II (managerial and technical occupations), III non-manual and III
17 199 manual (skilled workers), IV (partly skilled workers), and V (unskilled manual workers). For
18 200 men, social class was coded using their own occupation except when they were unemployed
19 201 or retired in which case their partner's social class was used. Unemployed men without
20 202 partners were unclassified. Social class in women was based on their partner's except when
21 203 the partner's social class was unclassified, missing, or they had no partner in which case
22 204 social class was based on their own occupation. An unemployed woman without a partner
23 205 was coded as unclassified. The final categorization of social class included manual: skilled
24 206 manual, partly skilled, and unskilled; and non-manual: professionals, managerial and
25 207 technical, and skilled non-manual. Employment was divided into yes vs. no.
26 208

27 209

28 209 Behaviour risk factor measures included alcohol intake (units of alcohol/week), smoking
29 210 status (current, former, non-smoker), and physical activity (inactive, moderately inactive,
30 211 moderately active, active). Presence of past-year DSM-IV major depressive disorder (MDD)
31 212 (yes/no) was also assessed.[39]
32 213

33 214

34 214 Individual-level health status was assessed through the construction of a variable capturing
35 215 major prevalent physical diseases associated with anxiety.[40] This was based on HLQ
36 216 questions asking participants: "Has the doctor ever told you that you have any of the
37 217 following?", followed by a list of options, such as stroke, myocardial infarction, and cancer.
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3 218 To determine disability levels, we used the physical component summary score (PCS) of the
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5 219 Medical Outcomes Study 36-Item Short Form (SF-36), a widely-used, validated self-
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7 220 assessment tool. A score of 100 represents no disability and 0 represents a high level of
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9 221 disability.[41] PCS scores were dichotomized above and below the median.

10 222

11 223 All of these individual-level variables were regarded as potential confounders and selected
12
13 224 based on the literature and their association with anxiety and health service use.[42, 43]
14

15 225

16 226 **Hospital service use**

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18 228 All analyses are based on non-psychiatric hospitalizations. Primary care service use was not
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20 229 captured in this study.
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22 230

23 231 Frequency of hospitalization between 1999/00 and 2009 was determined using
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25 232 administrative health databases maintained by the National Health Service. The East
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27 233 Norfolk Primary Health Care trust databases were used, and these are updated on an
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29 234 ongoing basis and provide information on clinical and administrative data from participating
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31 235 facilities, such as, hospitals.
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33 236

34 237 England is under a publicly-funded health care system (the National Health Service), free at
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36 238 the point of delivery; therefore, we expect factors, such as access to health insurance or
37
38 239 personal income, to have minimal impact on the care that is obtained by study participants.

39 240 The databases used in this study are maintained by the National Health Service, which is
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41 241 likely to capture most hospital admissions from the population, as private sector provision is
42
43 242 minimal. This means that admissions data in our study can be considered complete for the
44
45 243 ascertainment of hospital/health service use, and the likelihood of bias minimal. To access
46
47 244 hospital services in the UK, a referral is needed from the primary care practitioner, who acts
48
49 245 as a gate-keeper to secondary care.
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51 246

52 247 The East Norfolk Primary Health Care databases were linked to the EPIC-Norfolk cohort
53
54 248 using participants' unique National Health Service number, which allows complete record
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56 249 linkage across settings and calendar time.
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3 250 Vital status for participants was determined through record linkage with the United
4
5 251 Kingdom Office of National Statistics. Vital status was available for all participants. This
6
7 252 allowed us to exclude those who died before their health service use was ascertained.
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9 253

10 254 **Statistical Analysis**

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13 256 First, demographics, social class, medical and psychiatric conditions, and risk behaviours
14
15 257 were compared by GAD status - the chi-square test was used to determine whether
16
17 258 differences were statistically significant for categorical variables. Second, the mean number
18
19 259 of hospital admissions was determined for each characteristic/covariate - the Kruskal Wallis
20
21 260 test was used to determine statistical significance for categorical covariates with three or
22
23 261 more categories, while the Wilcoxon rank-sum test was used for dichotomous covariates.
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25 262

26 263 Since the number of hospital admissions was skewed and the variance was much larger than
27
28 264 the mean, zero-inflated negative binomial regression was used for frequency of hospital
29
30 265 utilization (number of hospital admissions). The log-likelihood test showed that this model
31
32 266 was superior to Poisson regression. Three models were fitted for hospital admissions with
33
34 267 progressive adjustment of covariates: model A adjusted for sociodemographics (age, sex,
35
36 268 education, marital status, social class, employment), physical conditions and disability;
37
38 269 model B further accounted for past-year MDD (assessed at the same questionnaire point as
39
40 270 past-year GAD); and model C further controlled for physical activity, alcohol, and smoking.
41
42 271 Multiple imputations for missing data were also carried out on the fully-adjusted model
43
44 272 assessing the association between past-year GAD and non-psychiatric hospitalization (our
45
46 273 primary objective).
47
48 274

49 275 Finally, we determined whether the risk for hospitalization was higher among those with: 1)
50
51 276 3 or more episodes of lifetime GAD (versus those with fewer than 3 episodes or no GAD), 2)
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53 277 episodes that lasted on average 6 months or more (versus those with fewer than 6 months
54
55 278 or no GAD), 3) age of onset at 30 years or younger (versus people with age at onset over 30
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57 279 years or no GAD), and 4) psychiatric comorbidity with MDD (versus no GAD-MDD
58
59 280 comorbidity). Two-sided statistical tests for the maximum likelihood zero inflation
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3 281 parameter estimates were conducted and a p-value of <0.05 was used for statistical
4 282 significance. Analyses were implemented in SAS, version 9.3.

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6 283

7
8 284 To arrive at the study size, we went through the following steps: of the 30,445 who
9 285 completed the baseline HLQ, we retained those participants who completed the HLEQ
10 286 (20,919), and of these, we kept those people with complete data on all covariates (17,939).
11 287 (Figure 1)

12
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15 16 17 18 289 **Patient involvement**

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21 291 There were no patients involved in the development of the research question and outcome
22 292 measures, the design of the study, or the recruitment to and conduct of the study.

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RESULTS

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296 Of the 30,445 people recruited at baseline, 20,919 participants completed the HLEQ; most
297 of the missing observations were from past-year GAD (479), past-year MDD (700), and
298 disability (1386); the rest of the missing observations were generated from the other
299 covariates (Figure 1). Notable findings from the missing data analysis show that people with
300 missing GAD more often had pre-existing health conditions, high disability, MDD, low
301 alcohol consumption, and were without employment (Appendix I).

302
303 The final sample included a total of 17,939 participants. Participants were assessed
304 between 1999/00 and 2009 (followed for 9 years) (Figure 1).

305
306 In 1996-2000, GAD was present in 393 out of 17,939 (2.2%) people. Table 1 shows the
307 baseline characteristics of participants by GAD status.

308

309 **Table 1 Percentage and number of people with past-year GAD reported in 1996-2000**
 310 **according to sociodemographic factors, health status, and behaviour risk factors for the**
 311 **EPIC-Norfolk cohort (n=17,939)**
 312

Characteristic	Number with characteristic	Percentage and number with past-year GAD
Socio-demographics		
Age (years)		
<50	2359	3.4 (79) ^a
50-60	6209	2.9 (179)
60-70	5733	1.6 (94)
70+	3638	1.1 (41)
Sex		
Women	9937	2.5 (249) ^b
Men	8002	1.8 (144)
Education[‡]		
Low	6106	2.0 (120) ^b
High	11833	2.3 (273)
Marital status		
Single	686	3.6 (25) ^a
Married	14538	2.0 (284)
Other*	2715	3.1 (84)
Social class		
Manual	6836	2.0 (137)
Non-manual	11103	2.3 (256)
Employment		
Yes	7712	2.0 (155)
No	10227	2.3 (238)
Health status		
Physical conditions[‡]		
Yes	9166	2.7 (251) ^a
No	8773	1.6 (142)
Disability level		
High [¶]	8900	3.0 (266) ^a
Low	9039	1.4 (127)
Psychiatric conditions		
Past-year MDD		
Yes	934	21.4 (200) ^a
No	17005	1.1 (193)
Behaviour risk factors		
Physical activity		
Active ^x	12822	2.1 (272)
Inactive	5117	2.4 (121)
Smoking status		
Current smoker	1893	4.7 (89) ^a
Former smoker	7470	1.9 (141)
Never smoker	8576	1.9 (163)
Alcohol intake		
High ^α	9241	2.0 (182) ^b

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Low	8698	2.4 (211)	313
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315 ‡ High education: O-level, A-level, degree; low education: refers to no education

316 * Other: divorced, separated, widowed

317 † Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart

318 attack, cancer, diabetes, thyroid conditions, arthritis

319 ¶ Below the median PCS value of 50.6

320 ‡ Moderately inactive, moderately active, active

321 ^a 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

322

323 ^a $P < 0.001$ 324 ^b $P < 0.05$

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3 325 Those with GAD were more likely to be younger, women, inactive, current smokers, low
4 326 alcohol consumers, of higher educational attainment, single, of non-manual social class,
5 327 without employment, with physical conditions, high levels of disability, and MDD. Table 2
6 328 summarizes the means and standard deviations of the number of hospital admissions by
7 329 participant characteristics.
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331 **Table 2: Non-psychiatric hospital admissions (mean, SD) by participant characteristics in**
 332 **17,939 British people between 1999/00 and 2009**

333

	Total number with characteristic	Number of admissions
Characteristic		Mean (SD)
Past-year GAD		
Yes	393	4.0 (6.3) ^a
No	17546	3.4 (13.0)
Socio-demographics		
Age (years)		
<50	2359	1.9 (9.8) ^a
50-60	6209	3.0 (16.5)
60-70	5733	3.8 (11.2)
70+	3638	4.6 (9.6)
Sex		
Women	9937	3.1 (14.0) ^a
Men	8002	3.9 (11.3)
Education[‡]		
Low	6106	4.1 (17.1) ^a
High	11833	3.1 (10.1)
Marital status		
Single	686	3.0 (8.9) ^a
Married	14538	3.3 (10.9)
Other*	2715	4.0 (21.0)
Social class		
Manual	6836	4.0 (18.3) ^a
Non-manual	11103	3.1 (7.8)
Employment		
Yes	7712	2.5 (9.1) ^a
No	10227	4.1 (15.1)
Health status		
Physical conditions[‡]		
Yes	9166	3.9 (10.4) ^a
No	8773	3.0 (15.1)
Disability level		
High [¶]	8900	4.4 (16.5) ^a
Low	9039	2.5 (7.8)
Psychiatric conditions		
Past-year MDD		
Yes	934	4.5 (13.6) ^a
No	17005	3.4 (12.9)
Behaviour risk factors		
Physical activity		
Active [‡]	12822	3.2 (13.3) ^a
Inactive	5117	4.1 (11.7)
Smoking status		
Current smoker	1893	4.6 (26.8) ^a

Former smoker	7470	3.8 (11.4)
Never smoker	8576	2.9 (8.6)
Alcohol intake		
High ^a	9241	3.2 (13.3) ^a
Low	8698	3.7 (12.5)

334

335 † High education: O-level, A-level, degree; low education: refers to no education

336 * Other: divorced, separated, widowed

337 † Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

338 † Below the median PCS value of 50.6

339 † Moderately inactive, moderately active, active

340 † 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

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342 ^a $P < 0.001$ 343 ^b $P < 0.05$

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3 346 Participants with GAD had a higher frequency of hospitalization compared to those without
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5 347 GAD. Some of the findings show that frequency of hospitalization was markedly higher
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7 348 among older age groups, men, those with low educational attainment, unemployed
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9 349 participants, those with high levels of disability, and with past-year MDD.

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11 351 Table 3 shows the unadjusted and adjusted incidence rate ratios of hospital admissions by
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13 352 GAD status.

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354 **Table 3: Associations between past-year GAD reported in 1996-2000 and non-psychiatric**
 355 **hospital admissions in 1999/00-2009 in 17,939 British people over the age of 40**
 356

Characteristic	IRR and 95% CI			
	Crude IRR	A ¹	B ²	C ³
Past-year GAD				
Yes	1.18 (1.02, 1.36)	1.25 (1.09, 1.43)	1.10 (0.96, 1.27)	1.04 (0.90, 1.20)
No	1.00	1.00	1.00	1.00
Socio-demographics				
Age				
Per 10 years	1.36 (1.33, 1.40)	1.19 (1.16, 1.23)	1.20 (1.17, 1.24)	1.21 (1.18, 1.25)
Sex				
Women	0.80 (0.76, 0.83)	0.76 (0.73, 0.79)	0.76 (0.72, 0.79)	0.78 (0.74, 0.81)
Men	1.00	1.00	1.00	1.00
Education[‡]				
Low	1.30 (1.24, 1.36)	1.13 (1.08, 1.18)	1.13 (1.08, 1.19)	1.11 (1.06, 1.16)
High	1.00	1.00	1.00	1.00
Marital status				
Single	0.88 (0.79, 0.99)	0.85 (0.77, 0.95)	0.85 (0.76, 0.95)	0.84 (0.76, 0.94)
Married	1.00	1.00	1.00	1.00
Other*	1.21 (1.14, 1.28)	1.17 (1.11, 1.24)	1.14 (1.07, 1.21)	1.09 (1.03, 1.16)
Social class				
Manual	1.29 (1.23, 1.34)	1.24 (1.19, 1.30)	1.24 (1.19, 1.30)	1.21 (1.16, 1.26)
Non-manual	1.00	1.00	1.00	1.00
Employment				
Yes	1.00	1.00	1.00	1.00
No	1.64 (1.57, 1.71)	1.18 (1.12, 1.25)	1.18 (1.12, 1.24)	1.15 (1.09, 1.21)
Health status				
Physical conditions[‡]				
Yes	1.32 (1.26, 1.37)	1.18 (1.13, 1.23)	1.17 (1.12, 1.22)	1.18 (1.13, 1.23)
No	1.00	1.00	1.00	1.00
Disability level				
High [¶]	1.78 (1.71, 1.86)	1.52 (1.45, 1.59)	1.51 (1.44, 1.57)	1.48 (1.42, 1.55)
Low	1.00	1.00	1.00	1.00
Psychiatric conditions				
Past-year MDD				
Yes	1.34 (1.22, 1.48)		1.34 (1.22, 1.48)	1.33 (1.21, 1.46)
No	1.00		1.00	1.00
Lifestyle				
Physical activity				
Active [‡]	1.00			1.00
Inactive	1.27 (1.21, 1.33)			1.04 (1.00, 1.09)
Smoking status				
Current smoker	1.60 (1.49, 1.72)			1.51 (1.41, 1.62)
Former smoker	1.33 (1.27, 1.39)			1.13 (1.08, 1.18)

Never smoker	1.00	1.00
Alcohol intake		
High ^α	0.88 (0.85, 0.92)	0.92 (0.88, 0.96)
Low	1.00	1.00

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¹ Model A: adjusted for sociodemographics (age, sex, education, marital status, social class, employment), physical conditions, disability

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² Model B: adjusted for sociodemographics, physical conditions, disability, MDD

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³ Model C: adjusted for sociodemographics, physical conditions, disability, MDD, physical activity, smoking, alcohol

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[‡] High education: O-level, A-level, degree; low education: refers to no education

365

^{*} Other: divorced, separated, widowed

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⁺ Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

367

368

[¶] Below the median PCS value of 50.6

369

[‡] Moderately inactive, moderately active, active

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^α 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

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3 373 After adjustment for sociodemographic variables, physical conditions, and disability, GAD
4 374 was associated with a 25% higher incidence rate of hospitalization (IRR=1.25, 95% CI: 1.09,
5 375 1.43). The incidence rate ratio was somewhat attenuated and became statistically non-
6 376 significant after further adjustment for MDD (IRR=1.10, 95% CI 0.96, 1.27). The effect
7 377 estimate approached the null after additional adjustment for behaviour risk factors
8 378 (IRR=1.04, 95% CI: 0.90, 1.20). Finally, we did multiple imputations for missing data
9 379 (Appendix II). The effect estimate remained the same when we imputed all covariates
10 380 except for GAD (IRR: 1.04, 95% CI: 1.02, 1.06). The effect estimate remained virtually
11 381 unchanged when we imputed all covariates including GAD (IRR: 1.05, 95% CI: 1.03, 1.08).
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22 384 Next, we assessed whether risk for hospital admissions varied by frequency of GAD lifetime
23 385 episodes, anxiety episode chronicity, GAD age of onset, and whether the hospitalization risk
24 386 was higher in those with psychiatric comorbidity (with MDD) (table 4). Results are based on
25 387 fully-adjusted models.
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389 **Table 4: Associations between different forms of GAD reported in 1996-2000 and non-**
 390 **psychiatric hospital admissions in 1999/00-2009 in 17,939 British people ages 40+**
 391

Characteristic	IRR and 95% CI			
GAD type				
Frequent GAD				
Yes ^a	1.07 (0.91, 1.27) ^e			
No	1.00			
Chronic GAD				
Yes ^b		1.07 (0.85, 1.35) ^e		
No		1.00		
Early age GAD onset				
Yes ^c			1.16 (0.95, 1.41) ^e	
No			1.00	
Comorbid GAD				
Yes ^d				1.23 (1.02, 1.49) ^e
No				1.00
Socio-demographics				
Age				
Per 10 years	1.22 (1.18, 1.25)	1.21 (1.18, 1.25)	1.22 (1.18, 1.25)	1.21 (1.17, 1.25)
Sex				
Women	0.78 (0.74, 0.81)	0.78 (0.74, 0.81)	0.78 (0.74, 0.81)	0.78 (0.75, 0.82)
Men	1.00	1.00	1.00	1.00
Education[‡]				
Low	1.10 (1.06, 1.16)	1.11 (1.06, 1.16)	1.10 (1.06, 1.16)	1.12 (1.07, 1.18)
High	1.00	1.00	1.00	1.00
Marital status				
Single	0.84 (0.76, 0.94)	0.84 (0.76, 0.94)	0.84 (0.76, 0.94)	0.83 (0.74, 0.93)
Married	1.00	1.00	1.00	1.00
Other [*]	1.10 (1.03, 1.16)	1.09 (1.03, 1.16)	1.09 (1.03, 1.16)	1.03 (0.97, 1.10)
Social class				
Manual	1.21 (1.16, 1.26)	1.21 (1.16, 1.26)	1.21 (1.16, 1.26)	1.21 (1.16, 1.27)
Non-manual	1.00	1.00	1.00	1.00
Employment				
Yes	1.00	1.00	1.00	1.00
No	1.15 (1.09, 1.21)	1.15 (1.09, 1.21)	1.15 (1.09, 1.21)	1.17 (1.11, 1.24)
Health status				
Physical conditions⁺				
Yes	1.17 (1.13, 1.23)	1.17 (1.13, 1.23)	1.17 (1.13, 1.23)	1.17 (1.12, 1.22)
No	1.00	1.00	1.00	1.00
Disability level				
High [¶]	1.48 (1.42, 1.55)	1.48 (1.42, 1.55)	1.48 (1.42, 1.55)	1.48 (1.42, 1.55)
Low	1.00	1.00	1.00	1.00
Psychiatric conditions				

Past-year MDD				
Yes	1.32 (1.20, 1.45)	1.33 (1.22, 1.46)	1.33 (1.21, 1.46)	--
No	1.00	1.00	1.00	
Lifestyle				
Physical activity				
Active [‡]	1.00	1.00	1.00	1.02 (0.97, 1.07)
Inactive	1.04 (1.00, 1.09)	1.04 (1.00, 1.09)	1.04 (1.00, 1.09)	1.00
Smoking status				
Current smoker	1.51 (1.41, 1.62)	1.51 (1.41, 1.62)	1.51 (1.41, 1.62)	1.56 (1.45, 1.68)
Former smoker	1.13 (1.08, 1.18)	1.13 (1.08, 1.18)	1.13 (1.08, 1.18)	1.14 (1.09, 1.19)
Never smoker	1.00	1.00	1.00	1.00
Alcohol intake				
High [¶]	0.92 (0.88, 0.96)	0.92 (0.88, 0.96)	0.92 (0.88, 0.96)	0.93 (0.89, 0.98)
Low	1.00	1.00	1.00	1.00

392

393

^a 3+ episodes of lifetime GAD

394

^b GAD episodes lasted at least 6 months

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^c GAD developed before 30 years of age

396

^d GAD-MDD comorbidity

397

^e Adjusted for sociodemographics, physical conditions, disability, MDD, physical activity, smoking, alcohol

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[‡] High education: O-level, A-level, degree; low education: refers to no education

400

^{*} Other: divorced, separated, widowed

401

[†] Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

402

403

[¶] Below the median PCS value of 50.6

404

[‡] Moderately inactive, moderately active, active

405

[¶] 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

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3 407 People with more than 3 lifetime episodes had a somewhat higher risk of hospitalization
4 408 (IRR=1.07, 95% CI: 0.91, 1.27). Those whose episodes lasted, on average, 6 months or
5 409 longer also had a slight increased risk for admissions compared to those with shorter
6 410 episodes (IRR=1.07, 95% CI: 0.85, 1.35). People who developed GAD before 30 years of age
7 411 were 16% more likely to be admitted to the hospital than those who developed it later in
8 412 life (IRR=1.16, 95% CI: 0.95, 1.41). Finally, we determined whether GAD comorbid with
9 413 MDD is associated with non-psychiatric hospital admissions. Results showed that people
10 414 with GAD-MDD comorbidity had a 23% higher chance of being admitted to hospital than
11 415 people without comorbidity – this association was statistically significant (IRR: 1.23 ,95% CI:
12 416 1.02, 1.49).
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DISCUSSION

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420 This is the first study to assess the association between GAD and hospital service use in a
421 population-based cohort. This longitudinal study showed that having an episode of GAD in
422 the past year was not independently associated with hospital admissions during the
423 subsequent ten years. However, those who developed GAD at an early age (before 30) and,
424 in particular, those with MDD comorbidity were at an increased risk of being admitted to
425 hospital than those with a later onset and without MDD comorbidity, respectively. The
426 association between GAD-MDD comorbidity and non-psychiatric hospital admissions was
427 statistically significant.

428
429 People with past-year GAD were more likely to have medical conditions; nonetheless,
430 including these covariates in the model left the association between past-year GAD and
431 hospital admissions statistically significant. It was only when MDD was introduced in the
432 model as a potential confounder that any remaining association with hospital service
433 utilization was explained away.

434

Strengths and limitations

436

437 There are several strengths associated with our study. We had a large, population-based
438 sample of middle- and older-aged adults and adequately adjusted for a range of possible
439 confounders. We used a structured questionnaire to assess past-year GAD according to
440 DSM-IV criteria, used large administrative health databases to examine hospital service use
441 (avoiding the self-reporting bias found in questionnaire studies), and participants were
442 followed for a long time. We had a large list of self-reported physician diagnoses of chronic
443 diseases that we used to ascertain medical histories. Despite this, the residual effect of
444 diseases not captured by our study, but that are associated with GAD may be present. Past
445 illness may have been underreported, which may have introduced measurement error and
446 further attenuated effect estimates towards the null. A negligible proportion of participants
447 may have obtained care at private facilities, which might have led to non-differential
448 misclassification. The databases used in this study also did not capture admissions to

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3 449 hospitals outside the UK. However, migration in the EPIC-Norfolk cohort is minimal and
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5 450 does not present a problem.

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8 452 We may have overadjusted our models with the inclusion of self-evaluated impairment, as
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10 453 this may be part of the expression of psychiatric illness. This can lead to attenuation of
11
12 454 effect estimates. If participants chose not to answer certain questions in the HLEQ, this
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14 455 contributed to missing data; however, to avoid biasing the findings, we retained participants
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16 456 for whom we had complete data on all covariates. Non-participation in our study also may
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18 457 have led to non-differential misclassification and further attenuation of effect estimates.

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21 459 Another limitation is that we did not have data on primary care service use. Merging
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23 460 population cohorts, such as ours, with primary care service administrative databases and
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25 461 hospitalization databases would have provided a more complete picture of the burden of
26
27 462 GAD on the health care system.

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29
30 464 This study was conducted on people ages 40 years and older and may not be generalizable
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32 465 to younger age groups. We suspect that the strength of the association between GAD-MDD
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34 466 comorbidity and non-psychiatric hospital admissions is weaker for younger populations who
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36 467 are typically healthier than older people. Although young people have a high burden of
37
38 468 mental health problems[40, 44], they (especially adolescents) are less likely to have non-
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40 469 psychiatric hospitalizations than older people[45]. It could take many years until the effects
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42 470 of anxiety comorbid with depression accumulate and manifest as poor physical health, thus
43
44 471 translating into higher use of non-psychiatric hospital services. As such, we would expect
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46 472 the strength of the association between GAD-MDD comorbidity and hospitalizations to be
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48 473 weaker in young people, however, future studies should investigate this.

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51 475 Participants were required to complete detailed dietary and lifestyle questionnaires and
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53 476 undergo periodic health assessments. Because those who participated in EPIC-Norfolk were
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55 477 more affluent and healthier than individuals living in other parts of England, our results may
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57 478 not generalize to people living in extremely deprived areas.

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3 480 Finally, there was missing data in this study. When we conducted multiple imputations for
4 481 missing data, the effect estimate of our main analysis remained unchanged.

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7 8 483 **Comparison with other studies**

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11 485 Most of the studies assessing the link between psychiatric disorders and non-psychiatric
12 486 health service utilization have focused on depression and, to a lesser extent, panic disorder
13 487 and PTSD, while other anxiety disorders have been significantly underresearched. Most of
14 488 the studies on depression as a stand alone measure have shown an association with health
15 489 service use in both clinical and community samples.[46] There are substantially fewer
16 490 studies on anxiety, and a number of these have shown positive associations with health
17 491 service use. A US study[47] that recruited patients from an outpatient clinic showed that
18 492 anxiety disorders were linked to higher utilization of primary care services compared to
19 493 depressive or addictive disorders. Patients, however, were recruited from an outpatient
20 494 clinic located in a predominantly rural area, which might have affected generalizability.
21 495 Another study showed anxiety disorders to be associated with a higher number of
22 496 consultations in general medical, emergency and specialty settings, such as cardiology and
23 497 dermatology.[48] In this study, people were sampled from an anxiety clinic, thereby leading
24 498 to possible selection bias. Other studies showed PTSD and GAD to be associated with health
25 499 care use, however, this research was based on highly-select samples that have limited
26 500 generalizability.[26, 28, 49, 50] In contrast to the literature, a major strength of our study
27 501 was that it was population-based. There is also a lack of research assessing whether the
28 502 severity of anxiety or different forms of the disorder contribute to even higher health
29 503 service use rates (early onset forms and comorbid cases are typically the most severe,
30 504 hardest to treat and with the poorest prognosis [9]).

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48 506 **Mechanisms**

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52 508 A more severe course of GAD can lead to higher rates of health services because of
53 509 unhealthy behaviours, such as smoking and alcohol (which we controlled for in our
54 510 analyses). It could also be that a more severe form of anxiety, such as GAD-MDD
55 511 comorbidity is associated with poorer underlying health, which then leads to higher health

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3 512 service use rates. Although we controlled for several chronic diseases, we might have
4 513 missed some conditions that are associated with GAD-MDD comorbidity and
5 514 hospitalizations. A third explanation for higher health service use in those with comorbid
6 515 anxiety and depression could relate to inflammatory pathways. If clinically apparent signs of
7 516 disease have not yet developed in those with psychiatric comorbidity or are at an early,
8 517 undetectable stage, it will not be possible to measure these factors and adjust for them in
9 518 analyses.

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16 17 520 **Implications**

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21 522 GAD is a debilitating and impairing condition.[9] The evidence base on its association with
22 523 health services is small and confined to clinical settings with the potential for self-selection
23 524 bias. Our study overcomes many limitations of previous studies, and clarifies that GAD
24 525 measured at a single point in time (ex. in the past year) is not associated with health service
25 526 use. Instead, it shows that cases with early age of GAD onset and especially those that are
26 527 comorbid with depression can lead to increased use of hospital services, after controlling for
27 528 a range of important confounders. In this study, GAD-MDD comorbidity was associated with
28 529 a statistically significantly increased risk of hospital admissions.

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36 531 Population-based research on anxiety is lacking, and thus far, no studies have assessed the
37 532 association between GAD and non-psychiatric hospitalization. Clinicians should consider
38 533 that it is not just the diagnosis of the disorder at one point in time that is predictive of
39 534 deleterious health outcomes; its long-term course and different forms of the disorder may
40 535 also be important. GAD has a waxing and waning course throughout a patient's life, and
41 536 many of those affected experience relapse after psychiatric treatment or develop
42 537 psychiatric comorbidities.

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50 539 Our findings are important for clinicians and policy-makers. Large numbers of people are
51 540 affected by anxiety-depression comorbidity and a number of individuals develop anxiety
52 541 early in life [9]. As such, clinicians should consider more widespread screening for mental
53 542 health problems and if appropriate, the examination of any underlying health conditions
54 543 that may require treatment in order to prevent future hospital admissions. Policy-makers

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3 544 should also consider rolling out more widespread anxiety prevention and screening
4 545 programmes.

5 546 Future research, however needs to examine the reasons for the increased non-psychiatric
6 547 hospital service use in those with GAD-MDD comorbidity (this can provide additional insight
7 548 into clinical recommendations). To provide a better understanding of the links between
8 549 mental and physical health, the bidirectional links between anxiety and physical health
9 550 problems should also be examined. Finally, future research should merge a population-
10 551 based cohort with primary and secondary care administrative health databases to provide a
11 552 more complete picture of the burden of different forms of anxiety on the health care
12 553 system.

13 554
14 555 Finally, while our association between early age of GAD onset and hospital admissions did
15 556 not reach statistical significance, the effect estimate does suggest that people who develop
16 557 anxiety early in life have a 16% higher chance of being admitted to hospital than those with
17 558 late-onset cases. Future research should replicate our study with a larger number of anxiety
18 559 cases by combining common anxiety disorders into one group.[22]

19 560

20 561 **Conclusion**

21 562

22 563 People with an earlier age of onset for GAD and especially those with comorbid MDD had a
23 564 higher risk for hospital admissions over 9 years between 1996-1999/00 and 2009 in the
24 565 European Prospective Investigation of Cancer in Norfolk study.

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21 580 versions of the paper; PS and NW provided feedback into the analysis. OR, CB, KK, LL, PS,
22 581 and NW contributed to the interpretation of data for the work, agreed to be accountable for
23 582 all aspects of the work, gave final approval of the version to be published, and made
24 583 substantial contributions to the analysis and interpretation of data. OR, CB, KK, LL, PS, and
25 584 NW have seen and approved the final version. OR, CB, KK, LL, PS, and NW had full access to
26 585 all the data in the study and take responsibility for the integrity of the data and the accuracy
27 586 of the data analysis. OR acts as guarantor of the study.

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30 588 Transparency declaration: OR affirms that the manuscript is an honest, accurate, and
31 589 transparent account of the study being reported; that no important aspects of the study
32 590 have been omitted; and that any discrepancies from the study as planned have been
33 591 explained.

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36 593 Role of study sponsors and statement of independence: The funding sources had no role in
37 594 the design and conduct of the study; collection, management, analysis, and interpretation of
38 595 the data; and preparation, review, or approval of the manuscript.

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3 597 Ethical approval: The study has ethics committee approval from Norfolk Ethics Committee
4 598 (Rec Ref: 98CN01) and all participants gave informed consent.

5 599 Data sharing: No additional data available. Original dataset requests should be sent to the
6 600 corresponding author. Please contact O Remes at or260@medschl.cam.ac.uk for questions
7 601 about the statistical code.

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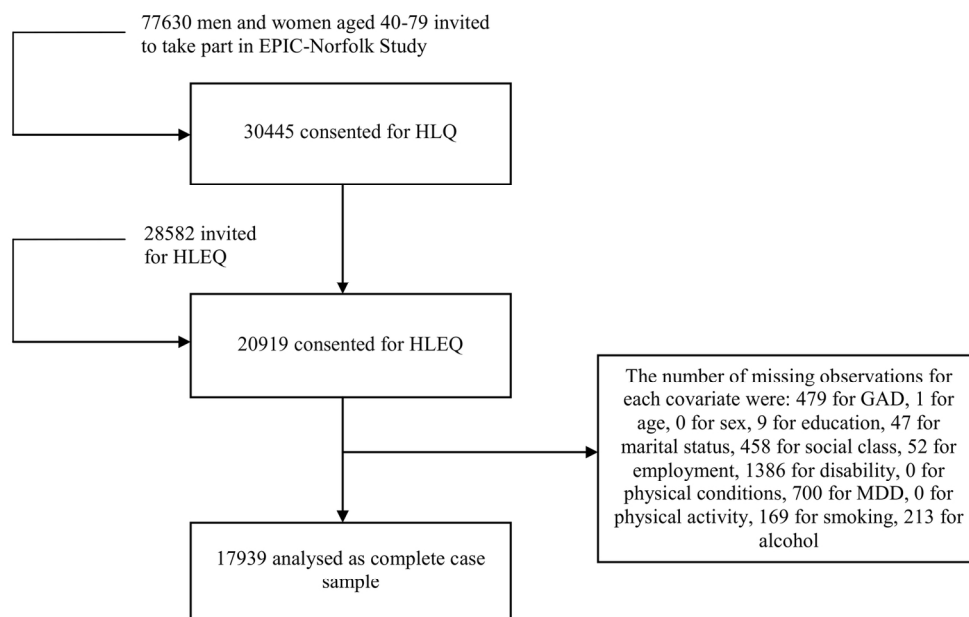
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3 773 **Figure 1 – Flowchart of EPIC-Norfolk cohort**

4 774 This is a flowchart showing the number of participants at each study stage: the number
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6 775 approached to participate in the EPIC-Norfolk study, the number enrolled at baseline, and
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8 776 with complete data on all covariates. The EPIC-Norfolk study consists of middle-aged and
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10 777 older British people.

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Figure 1 - Flowchart of EPIC-Norfolk cohort



Note: Some participants had missing observations on more than one covariate.

Flowchart of the European Prospective Investigation of Cancer (EPIC)-Norfolk cohort. This is a flowchart showing the number of participants at each study stage: the number approached to participate in the EPIC-Norfolk study, the number enrolled at baseline, and with complete data on all covariates. The EPIC-Norfolk study consists of middle-aged and older British people.

153x135mm (300 x 300 DPI)

Appendix I: Table 1 Percentage and number of people with missing past-year GAD reported in 1996-2000 according to sociodemographic factors, health status, and behaviour risk factors for the EPIC-Norfolk cohort

Characteristic	Total number with characteristic	Percentage and no. with missing past-year GAD
Socio-demographics		
Age (years)		
<50	2385	1.1 (26)
50-60	6279	1.1 (70)
60-70	5787	0.9 (54)
70+	3685	1.3 (47)
Sex		
Women	10055	1.2 (118)
Men	8081	1.0 (79)
Education[†]		
Low	6178	1.2 (72)
High	11958	1.1 (125)
Marital status		
Single	695	1.3 (9)
Married	14687	1.0 (149)
Other*	2754	1.4 (39)
Social class		
Manual	6918	1.2 (82)
Non-manual	11218	1.0 (115)
Employment		
Yes	7775	0.8 (63) ^b
No	10361	1.3 (134)
Health status		
Physical conditions⁺		
Yes	9285	1.3 (119) ^b
No	8851	0.9 (78)
Disability level		
High [¶]	9030	1.4 (130) ^a
Low	9106	0.7 (67)
Psychiatric conditions		
Past-year MDD		
Yes	983	5.0 (49) ^a
No	17153	0.9 (148)
Behaviour risk factors		
Physical activity		
Active [‡]	12963	1.1 (141)
Inactive	5173	1.1 (56)
Smoking status		
Current smoker	1922	1.5 (29)
Former smoker	7543	1.0 (73)

Never smoker	8671	1.1 (95)
Alcohol intake		
High ^a	9327	0.9 (86) ^b
Low	8809	1.3 (111)

‡ High education: O-level, A-level, degree; low education: refers to no education

* Other: divorced, separated, widowed

+ Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

¶ Below the median PCS value of 50.6

¥ Moderately inactive, moderately active, active

^a 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

^a $P < 0.001$

^b $P < 0.05$

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Appendix 2 – Multiple imputations for missing data

1. Main analysis: association between past-year GAD and non-psychiatric hospital admissions

First, we imputed missing data for all covariates except GAD, our main exposure. Based on the literature, we identified potential auxiliary variables, and we retained those that were correlated with the variables in our model and were good predictors of the missing status (based on statistical tests). Our imputation model included all variables from the analysis model and the auxiliary variables.

To retain as much information as possible, we conducted the imputations on non-transformed data—the original variables in our dataset. We imputed data using the fully conditional specification, and specified a linear regression model for continuous data that were normally distributed; predictive mean matching for continuous data that were not normally distributed; and logistic regression for categorical variables. Variable estimates were subsequently averaged from 100 imputed datasets using Rubin's rules (we transformed the data before running the analytic model of interest within each of the imputed datasets).¹

We checked whether the imputations were acceptable by comparing 1) the means, standard deviations, and plots of recorded and imputed values for continuous variables, and 2) the frequencies and percentages of recorded and imputed values for each level of categorical variables.

Analyses were done using SAS 9.3 and p-values less than 0.05 were considered statistically significant.

Findings from this set of multiple imputations for missing data analysis provided the following effect estimate relating past-year GAD and non-psychiatric hospital admissions: IRR: 1.04, 95% CI: 1.02, 1.06. The IRR of 1.04 was the same as in the complete case analysis.

The same process was repeated and we imputed missing data for all covariates and also for GAD. This was the effect estimate: IRR: 1.05, 95% CI: 1.03, 1.08.

2. Subsidiary analysis: association between GAD-MDD comorbidity and non-psychiatric hospital admissions

When different forms of GAD were considered in relation to health service use, the effect estimate for GAD-MDD comorbidity was the only one that emerged as statistically significant in the complete case analysis. Therefore, we repeated this analysis using multiple imputations for missing data (similar process to that described in the first instance – we imputed missing data for all covariates except for GAD and MDD) and obtained the following result: IRR=1.20, 95% CI: 1.18, 1.22. The IRR is very similar to that obtained in the complete case analysis.

Auxiliary variables used in the imputation models

Variable	Questionnaire	Description of variable
Sociodemographic factors		
History of psychiatric illness	Health and Lifestyle Questionnaire (HLQ)	Self-reported history of other psychiatric illness
History of back pain	Health and Lifestyle Questionnaire (HLQ)	Self-reported history of back pain
History of cholesterol	Health and Lifestyle Questionnaire (HLQ)	Self-reported history of cholesterol
History of migraine	Health and Lifestyle Questionnaire (HLQ)	Self-reported history of migraine
History of tumour	Health and Lifestyle Questionnaire (HLQ)	Self-reported history of tumour

The questionnaire used for these variables have been previously described in the methods.

References

1. Berglund P, Heeringa S. Multiple imputation of missing data using SAS. Cary, NC: SAS Institute Inc, 2014.

Please see the article line numbers (column on the right) and the explanations provided.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Line numbers within the article
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	9, 44 35-70
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	95-142
Objectives	3	State specific objectives, including any prespecified hypotheses	144-148
Methods			
Study design	4	Present key elements of study design early in the paper	156
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	155-166, 228-229
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	155-158, 160-162, 164-166, and especially 168-170
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Outcome: 223-246 Exposure: 172-182 Confounders: 183-221
Data sources/	8*	For each variable of interest, give sources of data and details of methods of	There were two variables of interest in this study:

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4 addressed

5 *Cross-sectional study*—If applicable, describe analytical methods taking account of
6 sampling strategy
7

various means, unless they expressed that they wished
to be removed from the mailing list. We elaborate on
this in the manuscript.

8 (e) Describe any sensitivity analyses
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Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	We do not have the reasons for non-participation, because these data were not collected when the study was initiated in 1993.
		(c) Consider use of a flow diagram	Flow diagram included in submission – figure 1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	302-303, 321-325, 342-345, as well as, tables 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	See flow diagram.
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	299-300
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	Table 2 provides the mean number of hospital admissions for those with/without GAD over the 9-year follow-up.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 3 and 4 contain unadjusted and progressively adjusted estimates. We also discussed the findings within the text, and provide odds ratios and 95% confidence intervals. We included the confounders based on the literature – we mention this in the paper and cite relevant literature. As per strobe, we included this information in the methods section; and we omitted repeating this in the results section to reduce redundancy. However, if the editor would like us to repeat this information in the results, we are happy to do so.

		(b) Report category boundaries when continuous variables were categorized	The cut-offs for age, alcohol intake, and disability levels are provided (see also footnotes of tables).
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	The Results section contains the findings from the multiple imputations for missing data analysis – we also included further information on this in an appendix. Findings for GAD frequency, chronicity, age of onset, and comorbidity with MDD are reported in table 4.
Discussion			
Key results	18	Summarise key results with reference to study objectives	416-422
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	438-476
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	514-551 (We also have a section comparing our study results to those of others: 478-499, as well as a section on potential mechanisms explaining our findings: 501-512)
Generalisability	21	Discuss the generalisability (external validity) of the study results	471-473, 549-468
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	567-568, 584-586

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Generalized anxiety disorder and non-psychiatric hospital admissions: findings from a large, population cohort study

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Generalized anxiety disorder and non-psychiatric hospital admissions: findings from a large, population cohort study

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Figures: 1; Tables: 4

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2
3 31 **ABSTRACT**
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5 33
6 34 **OBJECTIVE**

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8 35 Generalized anxiety disorder (GAD) is the most common anxiety disorder in the general
9 36 population, and has been associated with high economic and human burden. However, it
10 37 has been neglected in the health services literature. The objective of this study will be to
11 38 assess whether GAD leads to non-psychiatric hospital admissions using data from the
12 39 European Prospective Investigation of Cancer-Norfolk. Other aims include determining
13 40 whether early or late onset forms of the disorder, episode chronicity and frequency, and
14 41 comorbidity with major depressive disorder (MDD) contribute to non-psychiatric hospital
15 42 admissions.
16 43

17 44 **DESIGN**

18
19 45 Large, population study.
20 46

21 47 **SETTING**

22 48 UK population-based cohort.
23 49

24 50 **PARTICIPANTS**

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26 51 30,445 people over the age of 40 were recruited through general practice registers in
27 52 England. Of these, 20,919 completed a structured health and lifestyle questionnaire used to
28 53 assess GAD. Anxiety was examined in 1996-2000, and health service use was captured
29 54 between 1999/00 and 2009 through record linkage with large, administrative health
30 55 databases. 17,939 participants had complete data on covariates.
31 56

32 57 **MAIN OUTCOME MEASURE**

33
34 58 Past-year GAD defined according to the Diagnostic and Statistical Manual of Mental
35 59 Disorders, fourth edition.
36 60

37 61 **RESULTS**

38
39 62 In this study, 2.2% (393/17,939) respondents had GAD. Anxiety was not independently
40 63 associated with non-psychiatric hospital admissions (IRR=1.04, 95% CI: 0.90, 1.20) over nine
41 64 years. However, those whose anxiety was comorbid with depression showed a statistically
42 65 significantly increased risk for non-psychiatric hospital admissions (IRR=1.23, 95% CI: 1.02,
43 66 1.49).
44 67

45 68 **CONCLUSION**

46
47 69 People with GAD and MDD comorbidity were at an increased risk for hospital admissions.
48 70 Clinicians should consider that meeting criteria for a pure or individual disorder at one point
49 71 in time, such as past-year GAD does not necessarily predict deleterious health outcomes;
50 72 rather different forms of the disorder, such as comorbid cases might be of greater
51 73 importance.
52 74

53 75 Key words: Anxiety, anxiety disorders, health services
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3 76 **ARTICLE SUMMARY**
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5 77 **Strengths and limitations of this study**
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- 7
8 78 • We used a large, population-based sample of middle- and older-aged adults and
9 79 adjusted for a range of important confounders, such as, sociodemographic factors
10 80 and medical history.
11 81
12 82 • We used a structured, self-reported questionnaire to assess presence of past-year
13 83 GAD, and participants were followed for 9 years.
14 84
15 85 • We examined health services through record linkage with large, administrative
16 86 health databases.
17 87
18 88 • Those who participated in this study were somewhat less deprived and healthier
19 89 than individuals living in other parts of England; therefore, our results may not
20 90 generalize to people living in extremely deprived circumstances.
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INTRODUCTION

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95 Anxiety disorders[1] are the most common class of psychiatric disorders in the general
96 population. The Global Burden of Disease study[2] estimated that anxiety disorders
97 contribute to 26.8 million disability adjusted life years, and their annual direct cost is \$42.3
98 billion[3]. Generalized anxiety disorder (GAD) is characterized by excessive, pervasive
99 worry, and a number of additional symptoms, such as restlessness and muscle tension. It is
100 a prevalent and disabling condition in adults, and can lead to serious impairment in social
101 and occupational functioning.[4] GAD is associated with poor quality of life, impaired
102 functioning and risk of suicide.[5-8] Across the anxiety disorders, this condition has been
103 found to be the most debilitating.[5, 9] Although there is effective treatment for GAD, only
104 a third of those affected receive any treatment.[8] This is because anxiety disorders are
105 frequently under-recognized and mismanaged by clinicians in primary care, which is often
106 the first point of contact for those with mental health problems.[10]

107

108 Although detection of anxiety in clinical settings is poor[11, 12] and the presence of
109 undiagnosed mental health problems can contribute to further emotional distress in
110 patients down the line[12], it could be that disorders such as GAD represent more than just
111 psychological or worry-related symptoms. It may be that anxiety symptoms are masking
112 underlying poor physical health or could be an early warning signal for future health
113 problems that are not yet detectable by standard medical tests. Such problems cannot be
114 simply resolved through psychological therapies or psychotropic medication.

115

116 Anxiety has been linked to hypothalamic-pituitary-adrenal (HPA)-axis dysregulation and
117 inflammation, and this can lead to poor health.[9] A recent study of hospitalized
118 patients[13] also showed that people with anxiety disorders had more co-morbid physical
119 conditions, including cardiovascular diseases and their risk factors, compared to people
120 without anxiety disorders. Conversely, anxiety could also represent a response to
121 underlying medical illness, and physical illness can exacerbate anxiety; the possibility of a
122 bidirectional relationship between anxiety and physical health should not be excluded.[14,
123 15] Compelling evidence from prospective studies, however, has shown that anxiety can

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3 124 indeed increase the risk of serious chronic conditions, such as cancer[16] and coronary heart
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5 125 disease (CHD)[17].

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7 126 When investigating the links between mental disorders and health outcomes, early or late-
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9 127 onset forms of anxiety disorders, as well as psychiatric comorbidity should be also
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11 128 considered. A study[18] of over one million Swedish men followed for over 20 years
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13 129 showed that early-onset forms of mental disorders in particular led to increased risk of
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15 130 incident CHD. Anxiety disorders, such as, GAD are also frequently comorbid with major
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17 131 depressive disorder (MDD)[19], and psychiatric comorbidity has been associated with
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19 132 poorer quality of life, worse prognosis, and higher use of health services for mental health
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21 133 problems than pure forms of the disorder.[20, 21, 22] Therefore, identifying clinical aspects,
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23 134 such as, early or late onset forms of the condition, episode chronicity and frequency, and
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25 135 comorbidity with MDD can lead to better clinical management and more accurate
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27 136 prediction of future disability and health service use.[23]

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30
31 138 GAD is one of the most common anxiety disorders in the general population[24] and the
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33 139 primary care setting[25], and has been associated with high economic and human burden.
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35 140 However, it has been neglected in the health services literature, with the exception of some
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37 141 studies showing GAD to contribute to higher use of primary care services in primary care
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39 142 samples.[26-29] Clinical samples, however, have the potential for self-selection bias.
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41 143 Whether GAD leads to non-psychiatric hospital admissions is unknown.

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45 145 The objective of this study will be to assess the association between GAD and non-
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47 146 psychiatric hospital admissions in a longitudinal, population cohort of over 18,000 British
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49 147 individuals followed for 9 years. The aim is also to determine whether early or late onset
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51 148 forms of the disorder, episode frequency and chronicity, and comorbidity with MDD
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53 149 contribute to non-psychiatric hospital admissions.

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METHODS

Study population

The study population was drawn from the European Prospective Investigation of Cancer-Norfolk longitudinal, cohort study, described in detail elsewhere.[30, 31] Briefly, a total of 30,445 participants over the age of 40 living in Norwich and the surrounding towns and rural areas were recruited between 1993 and 1997 using general practice registers. At baseline, they completed a health questionnaire capturing sociodemographics and medical history. During follow-up, between 1993 and 1999/2000, participants completed self-reported postal questionnaires provided they: 1) were still alive, 2) did not ask to be removed from the study's mailing list, and 3) had a valid mailing address. Between 1996 and 1999/2000, respondents completed a Health and Life Experiences Questionnaire (HLEQ)[30] used to capture information on psychiatric disorders, other psychosocial factors, and risk behaviours. Record linkage with administrative health databases using a unique identifier was used to determine hospitalization admissions data until 2009.

All participants recruited through general-practice registers and who completed a baseline health questionnaire were eligible to be included in our study; those who completed a psychosocial questionnaire during follow-up were eligible to be included in our analysis.

Assessment of GAD

The HLEQ was used to derive a measure of GAD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition. The HLEQ captured the onset and offset timings of episodes of past-year GAD.[32] Past-year GAD consisted of at least one episode that had offset within 12 months of administration of the HLEQ. DSM-IV GAD was diagnosed if participants reported having uncontrollable, excessive worry for six months or longer on most days than not that resulted in disability or impairment. In addition, at least three of the following symptoms needed to have been present: restlessness, irritability, muscle tension, fatigue, trouble concentrating because of worry, mind going blank, trouble falling asleep, trouble staying asleep, and feeling keyed up or on edge.

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3 184 **Assessment of covariates**
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6 186 Potential confounders (based on the literature) included sociodemographics (age, sex,
7 187 education, marital status, social class, employment), prevalent physical diseases, disability,
8 188 MDD, and risk behaviours (alcohol use, smoking, physical activity). The final categorization
9 189 of the variables took cell size into account and was also done in accordance with previous
10 190 literature.[32, 33-38] Age was first assessed as a categorical variable, and subsequently
11 191 divided into 10-year bands. Sex was categorized into male vs. female; marital status was
12 192 categorized into: married, single (or never married), and others (widowed, divorced,
13 193 separated); educational attainment into high (vocational or formal qualifications at the A- or
14 194 O-level or degree-level qualifications) vs. low (no formal qualifications). Social class was
15 195 derived using the Computer-Assisted Standard Occupational Coding[38] and categorized as
16 196 follows: I (professionals), II (managerial and technical occupations), III non-manual and III
17 197 manual (skilled workers), IV (partly skilled workers), and V (unskilled manual workers). For
18 198 men, social class was coded using their own occupation except when they were unemployed
19 199 or retired in which case their partner's social class was used. Unemployed men without
20 200 partners were unclassified. Social class in women was based on their partner's except when
21 201 the partner's social class was unclassified, missing, or they had no partner in which case
22 202 social class was based on their own occupation. An unemployed woman without a partner
23 203 was coded as unclassified. The final categorization of social class included manual: skilled
24 204 manual, partly skilled, and unskilled; and non-manual: professionals, managerial and
25 205 technical, and skilled non-manual. Employment was divided into yes vs. no.
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43 207 Behaviour risk factor measures included alcohol intake (units of alcohol/week), smoking
44 208 status (current, former, non-smoker), and physical activity (inactive, moderately inactive,
45 209 moderately active, active). Presence of past-year DSM-IV major depressive disorder (MDD)
46 210 (yes/no) was also assessed.[39]
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52 212 Individual-level health status was assessed through the construction of a variable capturing
53 213 major prevalent physical diseases associated with anxiety.[40] This was based on HLQ
54 214 questions asking participants: "Has the doctor ever told you that you have any of the
55 215 following?", followed by a list of options, such as stroke, myocardial infarction, and cancer.
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3 216 To determine disability levels, we used the physical component summary score (PCS) of the
4 217 Medical Outcomes Study 36-Item Short Form (SF-36), a widely-used, validated self-
5 218 assessment tool. A score of 100 represents no disability and 0 represents a high level of
6 219 disability.[41] PCS scores were dichotomized above and below the median.
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10 220

11 221 All of these individual-level variables were regarded as potential confounders and selected
12 222 based on the literature and their association with anxiety and health service use.[42, 43]
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15 223

16 224 **Hospital service use**

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18 226 All analyses are based on non-psychiatric hospitalizations. Primary care service use was not
19 227 captured in this study.
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23 229 Frequency of hospitalization between 1999/00 and 2009 was determined using
24 230 administrative health databases maintained by the National Health Service. The East
25 231 Norfolk Primary Health Care trust databases were used, and these are updated on an
26 232 ongoing basis and provide information on clinical and administrative data from participating
27 233 facilities, such as, hospitals.
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31 235 England is under a publicly-funded health care system (the National Health Service), free at
32 236 the point of delivery; therefore, we expect factors, such as access to health insurance or
33 237 personal income, to have minimal impact on the care that is obtained by study participants.
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35

36 238 The databases used in this study are maintained by the National Health Service, which is
37 239 likely to capture most hospital admissions from the population, as private sector provision is
38 240 minimal. This means that admissions data in our study can be considered complete for the
39 241 ascertainment of hospital/health service use, and the likelihood of bias minimal. To access
40 242 hospital services in the UK, a referral is needed from the primary care practitioner, who acts
41 243 as a gate-keeper to secondary care.
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45 245 The East Norfolk Primary Health Care databases were linked to the EPIC-Norfolk cohort
46 246 using participants' unique National Health Service number, which allows complete record
47 247 linkage across settings and calendar time.
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3 248 Vital status for participants was determined through record linkage with the United
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5 249 Kingdom Office of National Statistics. Vital status was available for all participants. This
6
7 250 allowed us to exclude those who died before their health service use was ascertained.
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10 252 **Statistical Analysis**

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13 254 First, demographics, social class, medical and psychiatric conditions, and risk behaviours
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15 255 were compared by GAD status - the chi-square test was used to determine whether
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17 256 differences were statistically significant for categorical variables. Second, the mean number
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19 257 of hospital admissions was determined for each characteristic/covariate - the Kruskal Wallis
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21 258 test was used to determine statistical significance for categorical covariates with three or
22
23 259 more categories, while the Wilcoxon rank-sum test was used for dichotomous covariates.
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25 260

26 261 Since the number of hospital admissions was skewed and the variance was much larger than
27
28 262 the mean, zero-inflated negative binomial regression was used for frequency of hospital
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30 263 utilization (number of hospital admissions). The log-likelihood test showed that this model
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32 264 was superior to Poisson regression. Three models were fitted for hospital admissions with
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34 265 progressive adjustment of covariates: model A adjusted for sociodemographics (age, sex,
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36 266 education, marital status, social class, employment), physical conditions and disability;
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38 267 model B further accounted for past-year MDD (assessed at the same questionnaire point as
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40 268 past-year GAD); and model C further controlled for physical activity, alcohol, and smoking.
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42 269 Multiple imputations for missing data were also carried out on the fully-adjusted model
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44 270 assessing the association between past-year GAD and non-psychiatric hospitalization (our
45
46 271 primary objective).
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48 272

49 273 Finally, we determined whether the risk for hospitalization was higher among those with: 1)
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51 274 3 or more episodes of lifetime GAD (versus those with fewer than 3 episodes or no GAD), 2)
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53 275 episodes that lasted on average 6 months or more (versus those with fewer than 6 months
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55 276 or no GAD), 3) age of onset at 30 years or younger (versus people with age at onset over 30
56
57 277 years or no GAD), and 4) psychiatric comorbidity with MDD (versus no GAD-MDD
58
59 278 comorbidity). Two-sided statistical tests for the maximum likelihood zero inflation
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3 279 parameter estimates were conducted and a p-value of <0.05 was used for statistical
4 280 significance. Analyses were implemented in SAS, version 9.3.

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7
8 282 To arrive at the study size, we went through the following steps: of the 30,445 who
9 283 completed the baseline HLQ, we retained those participants who completed the HLEQ
10 284 (20,919), and of these, we kept those people with complete data on all covariates (17,939).
11 285 (Figure 1)

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15 16 17 18 287 **Patient involvement**

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21 289 There were no patients involved in the development of the research question and outcome
22 290 measures, the design of the study, or the recruitment to and conduct of the study.

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RESULTS

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294 Of the 30,445 people recruited at baseline, 20,919 participants completed the HLEQ; most
295 of the missing observations were from past-year GAD (479), past-year MDD (700), and
296 disability (1386); the rest of the missing observations were generated from the other
297 covariates (Figure 1). Notable findings from the missing data analysis show that people with
298 missing GAD more often had pre-existing health conditions, high disability, MDD, low
299 alcohol consumption, and were without employment (Appendix I).

300
301 The final sample included a total of 17,939 participants. Participants were assessed
302 between 1999/00 and 2009 (followed for 9 years) (Figure 1).

303
304 In 1996-2000, GAD was present in 393 out of 17,939 (2.2%) people. Table 1 shows the
305 baseline characteristics of participants by GAD status.

306

307 **Table 1 Percentage and number of people with past-year GAD reported in 1996-2000**
 308 **according to sociodemographic factors, health status, and behaviour risk factors for the**
 309 **EPIC-Norfolk cohort (n=17,939)**
 310

Characteristic	Number with characteristic	Percentage and number with past-year GAD
Socio-demographics		
Age (years)		
<50	2359	3.4 (79) ^a
50-60	6209	2.9 (179)
60-70	5733	1.6 (94)
70+	3638	1.1 (41)
Sex		
Women	9937	2.5 (249) ^b
Men	8002	1.8 (144)
Education[‡]		
Low	6106	2.0 (120) ^b
High	11833	2.3 (273)
Marital status		
Single	686	3.6 (25) ^a
Married	14538	2.0 (284)
Other [*]	2715	3.1 (84)
Social class		
Manual	6836	2.0 (137)
Non-manual	11103	2.3 (256)
Employment		
Yes	7712	2.0 (155)
No	10227	2.3 (238)
Health status		
Physical conditions[†]		
Yes	9166	2.7 (251) ^a
No	8773	1.6 (142)
Disability level		
High [¶]	8900	3.0 (266) ^a
Low	9039	1.4 (127)
Psychiatric conditions		
Past-year MDD		
Yes	934	21.4 (200) ^a
No	17005	1.1 (193)
Behaviour risk factors		
Physical activity		
Active ^x	12822	2.1 (272)
Inactive	5117	2.4 (121)
Smoking status		
Current smoker	1893	4.7 (89) ^a
Former smoker	7470	1.9 (141)
Never smoker	8576	1.9 (163)
Alcohol intake		
High ^α	9241	2.0 (182) ^b

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Low	8698	2.4 (211)	311
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313 ‡ High education: O-level, A-level, degree; low education: refers to no education

314 * Other: divorced, separated, widowed

315 † Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart

316 attack, cancer, diabetes, thyroid conditions, arthritis

317 ¶ Below the median PCS value of 50.6

318 ‡ Moderately inactive, moderately active, active

319 ^a 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

320

321 ^a $P < 0.001$ 322 ^b $P < 0.05$

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3 323 Those with GAD were more likely to be younger, women, inactive, current smokers, low
4 324 alcohol consumers, of higher educational attainment, single, of non-manual social class,
5 325 without employment, with physical conditions, high levels of disability, and MDD. Table 2
6 326 summarizes the means and standard deviations of the number of hospital admissions by
7 327 participant characteristics.
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329 **Table 2: Non-psychiatric hospital admissions (mean, SD) by participant characteristics in**
 330 **17,939 British people between 1999/00 and 2009**

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	Total number with characteristic	Number of admissions
Characteristic		Mean (SD)
Past-year GAD		
Yes	393	4.0 (6.3) ^a
No	17546	3.4 (13.0)
Socio-demographics		
Age (years)		
<50	2359	1.9 (9.8) ^a
50-60	6209	3.0 (16.5)
60-70	5733	3.8 (11.2)
70+	3638	4.6 (9.6)
Sex		
Women	9937	3.1 (14.0) ^a
Men	8002	3.9 (11.3)
Education[‡]		
Low	6106	4.1 (17.1) ^a
High	11833	3.1 (10.1)
Marital status		
Single	686	3.0 (8.9) ^a
Married	14538	3.3 (10.9)
Other*	2715	4.0 (21.0)
Social class		
Manual	6836	4.0 (18.3) ^a
Non-manual	11103	3.1 (7.8)
Employment		
Yes	7712	2.5 (9.1) ^a
No	10227	4.1 (15.1)
Health status		
Physical conditions[‡]		
Yes	9166	3.9 (10.4) ^a
No	8773	3.0 (15.1)
Disability level		
High [¶]	8900	4.4 (16.5) ^a
Low	9039	2.5 (7.8)
Psychiatric conditions		
Past-year MDD		
Yes	934	4.5 (13.6) ^a
No	17005	3.4 (12.9)
Behaviour risk factors		
Physical activity		
Active [‡]	12822	3.2 (13.3) ^a
Inactive	5117	4.1 (11.7)
Smoking status		
Current smoker	1893	4.6 (26.8) ^a

Former smoker	7470	3.8 (11.4)
Never smoker	8576	2.9 (8.6)
Alcohol intake		
High ^a	9241	3.2 (13.3) ^a
Low	8698	3.7 (12.5)

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333 † High education: O-level, A-level, degree; low education: refers to no education

334 * Other: divorced, separated, widowed

335 † Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

337 ¶ Below the median PCS value of 50.6

338 ¥ Moderately inactive, moderately active, active

339 ^a 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

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341 ^a $P < 0.001$ 342 ^b $P < 0.05$

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3 344 Participants with GAD had a higher frequency of hospitalization compared to those without
4
5 345 GAD. Some of the findings show that frequency of hospitalization was markedly higher
6
7 346 among older age groups, men, those with low educational attainment, unemployed
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9 347 participants, those with high levels of disability, and with past-year MDD.

10 348

11 349 Table 3 shows the unadjusted and adjusted incidence rate ratios of hospital admissions by

12 350 GAD status.

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352 **Table 3: Associations between past-year GAD reported in 1996-2000 and non-psychiatric**
 353 **hospital admissions in 1999/00-2009 in 17,939 British people over the age of 40**
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IRR and 95% CI				
Characteristic	Crude IRR	A ¹	B ²	C ³
Past-year GAD				
Yes	1.18 (1.02, 1.36)	1.25 (1.09, 1.43)	1.10 (0.96, 1.27)	1.04 (0.90, 1.20)
No	1.00	1.00	1.00	1.00
Socio-demographics				
Age				
Per 10 years	1.36 (1.33, 1.40)	1.19 (1.16, 1.23)	1.20 (1.17, 1.24)	1.21 (1.18, 1.25)
Sex				
Women	0.80 (0.76, 0.83)	0.76 (0.73, 0.79)	0.76 (0.72, 0.79)	0.78 (0.74, 0.81)
Men	1.00	1.00	1.00	1.00
Education[‡]				
Low	1.30 (1.24, 1.36)	1.13 (1.08, 1.18)	1.13 (1.08, 1.19)	1.11 (1.06, 1.16)
High	1.00	1.00	1.00	1.00
Marital status				
Single	0.88 (0.79, 0.99)	0.85 (0.77, 0.95)	0.85 (0.76, 0.95)	0.84 (0.76, 0.94)
Married	1.00	1.00	1.00	1.00
Other*	1.21 (1.14, 1.28)	1.17 (1.11, 1.24)	1.14 (1.07, 1.21)	1.09 (1.03, 1.16)
Social class				
Manual	1.29 (1.23, 1.34)	1.24 (1.19, 1.30)	1.24 (1.19, 1.30)	1.21 (1.16, 1.26)
Non-manual	1.00	1.00	1.00	1.00
Employment				
Yes	1.00	1.00	1.00	1.00
No	1.64 (1.57, 1.71)	1.18 (1.12, 1.25)	1.18 (1.12, 1.24)	1.15 (1.09, 1.21)
Health status				
Physical conditions[‡]				
Yes	1.32 (1.26, 1.37)	1.18 (1.13, 1.23)	1.17 (1.12, 1.22)	1.18 (1.13, 1.23)
No	1.00	1.00	1.00	1.00
Disability level				
High [¶]	1.78 (1.71, 1.86)	1.52 (1.45, 1.59)	1.51 (1.44, 1.57)	1.48 (1.42, 1.55)
Low	1.00	1.00	1.00	1.00
Psychiatric conditions				
Past-year MDD				
Yes	1.34 (1.22, 1.48)		1.34 (1.22, 1.48)	1.33 (1.21, 1.46)
No	1.00		1.00	1.00
Lifestyle				
Physical activity				
Active [‡]	1.00			1.00
Inactive	1.27 (1.21, 1.33)			1.04 (1.00, 1.09)
Smoking status				
Current smoker	1.60 (1.49, 1.72)			1.51 (1.41, 1.62)
Former smoker	1.33 (1.27, 1.39)			1.13 (1.08, 1.18)

Never smoker	1.00	1.00
Alcohol intake		
High ^α	0.88 (0.85, 0.92)	0.92 (0.88, 0.96)
Low	1.00	1.00

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¹ Model A: adjusted for sociodemographics (age, sex, education, marital status, social class, employment), physical conditions, disability

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² Model B: adjusted for sociodemographics, physical conditions, disability, MDD

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³ Model C: adjusted for sociodemographics, physical conditions, disability, MDD, physical activity, smoking, alcohol

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[‡] High education: O-level, A-level, degree; low education: refers to no education

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^{*} Other: divorced, separated, widowed

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⁺ Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

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[¶] Below the median PCS value of 50.6

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[‡] Moderately inactive, moderately active, active

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^α 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

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3 371 After adjustment for sociodemographic variables, physical conditions, and disability, GAD
4 372 was associated with a 25% higher incidence rate of hospitalization (IRR=1.25, 95% CI: 1.09,
5 373 1.43). The incidence rate ratio was somewhat attenuated and became statistically non-
6 374 significant after further adjustment for MDD (IRR=1.10, 95% CI 0.96, 1.27). The effect
7 375 estimate approached the null after additional adjustment for behaviour risk factors
8 376 (IRR=1.04, 95% CI: 0.90, 1.20). Finally, we did multiple imputations for missing data
9 377 (Appendix II). The effect estimate remained the same when we imputed all covariates
10 378 except for GAD (IRR: 1.04, 95% CI: 1.02, 1.06). The effect estimate remained virtually
11 379 unchanged when we imputed all covariates including GAD (IRR: 1.05, 95% CI: 1.03, 1.08).
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382 Next, we assessed whether risk for hospital admissions varied by frequency of GAD lifetime
383 episodes, anxiety episode chronicity, GAD age of onset, and whether the hospitalization risk
384 was higher in those with psychiatric comorbidity (with MDD) (table 4). Results are based on
385 fully-adjusted models.

386

387 **Table 4: Associations between different forms of GAD reported in 1996-2000 and non-**
 388 **psychiatric hospital admissions in 1999/00-2009 in 17,939 British people ages 40+**
 389

Characteristic	IRR and 95% CI			
GAD type				
Frequent GAD				
Yes ^a	1.07 (0.91, 1.27) ^e			
No	1.00			
Chronic GAD				
Yes ^b		1.07 (0.85, 1.35) ^e		
No		1.00		
Early age GAD onset				
Yes ^c			1.16 (0.95, 1.41) ^e	
No			1.00	
Comorbid GAD				
Yes ^d				1.23 (1.02, 1.49) ^e
No				1.00
Socio-demographics				
Age				
Per 10 years	1.22 (1.18, 1.25)	1.21 (1.18, 1.25)	1.22 (1.18, 1.25)	1.21 (1.17, 1.25)
Sex				
Women	0.78 (0.74, 0.81)	0.78 (0.74, 0.81)	0.78 (0.74, 0.81)	0.78 (0.75, 0.82)
Men	1.00	1.00	1.00	1.00
Education[‡]				
Low	1.10 (1.06, 1.16)	1.11 (1.06, 1.16)	1.10 (1.06, 1.16)	1.12 (1.07, 1.18)
High	1.00	1.00	1.00	1.00
Marital status				
Single	0.84 (0.76, 0.94)	0.84 (0.76, 0.94)	0.84 (0.76, 0.94)	0.83 (0.74, 0.93)
Married	1.00	1.00	1.00	1.00
Other [*]	1.10 (1.03, 1.16)	1.09 (1.03, 1.16)	1.09 (1.03, 1.16)	1.03 (0.97, 1.10)
Social class				
Manual	1.21 (1.16, 1.26)	1.21 (1.16, 1.26)	1.21 (1.16, 1.26)	1.21 (1.16, 1.27)
Non-manual	1.00	1.00	1.00	1.00
Employment				
Yes	1.00	1.00	1.00	1.00
No	1.15 (1.09, 1.21)	1.15 (1.09, 1.21)	1.15 (1.09, 1.21)	1.17 (1.11, 1.24)
Health status				
Physical conditions⁺				
Yes	1.17 (1.13, 1.23)	1.17 (1.13, 1.23)	1.17 (1.13, 1.23)	1.17 (1.12, 1.22)
No	1.00	1.00	1.00	1.00
Disability level				
High [¶]	1.48 (1.42, 1.55)	1.48 (1.42, 1.55)	1.48 (1.42, 1.55)	1.48 (1.42, 1.55)
Low	1.00	1.00	1.00	1.00
Psychiatric conditions				

Past-year MDD				
Yes	1.32 (1.20, 1.45)	1.33 (1.22, 1.46)	1.33 (1.21, 1.46)	--
No	1.00	1.00	1.00	
Lifestyle				
Physical activity				
Active [‡]	1.00	1.00	1.00	1.02 (0.97, 1.07)
Inactive	1.04 (1.00, 1.09)	1.04 (1.00, 1.09)	1.04 (1.00, 1.09)	1.00
Smoking status				
Current smoker	1.51 (1.41, 1.62)	1.51 (1.41, 1.62)	1.51 (1.41, 1.62)	1.56 (1.45, 1.68)
Former smoker	1.13 (1.08, 1.18)	1.13 (1.08, 1.18)	1.13 (1.08, 1.18)	1.14 (1.09, 1.19)
Never smoker	1.00	1.00	1.00	1.00
Alcohol intake				
High [¶]	0.92 (0.88, 0.96)	0.92 (0.88, 0.96)	0.92 (0.88, 0.96)	0.93 (0.89, 0.98)
Low	1.00	1.00	1.00	1.00

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^a 3+ episodes of lifetime GAD

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^b GAD episodes lasted at least 6 months

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^c GAD developed before 30 years of age

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^d GAD-MDD comorbidity

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^e Adjusted for sociodemographics, physical conditions, disability, MDD, physical activity, smoking, alcohol

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[‡] High education: O-level, A-level, degree; low education: refers to no education

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^{*} Other: divorced, separated, widowed

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[†] Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

400

[¶] Below the median PCS value of 50.6

401

402

[‡] Moderately inactive, moderately active, active

403

[¶] 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

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3 405 People with more than 3 lifetime episodes had a somewhat higher risk of hospitalization
4 406 (IRR=1.07, 95% CI: 0.91, 1.27). Those whose episodes lasted, on average, 6 months or
5 407 longer also had a slight increased risk for admissions compared to those with shorter
6 408 episodes (IRR=1.07, 95% CI: 0.85, 1.35). People who developed GAD before 30 years of age
7 409 were 16% more likely to be admitted to the hospital than those who developed it later in
8 410 life (IRR=1.16, 95% CI: 0.95, 1.41), although this finding was not statistically significant.
9 411 Finally, we determined whether GAD comorbid with MDD is associated with non-psychiatric
10 412 hospital admissions. Results showed that people with GAD-MDD comorbidity had a 23%
11 413 higher chance of being admitted to hospital than people without comorbidity – this
12 414 association was statistically significant (IRR: 1.23 ,95% CI: 1.02, 1.49).
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DISCUSSION

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418 This is the first study to assess the association between GAD and hospital service use in a
419 population-based cohort. This longitudinal study showed that having an episode of GAD in
420 the past year was not independently associated with hospital admissions during the
421 subsequent nine years. Chronic GAD (at least 6 months), frequent GAD (at least 3 lifetime
422 episodes), and anxiety with an early age of onset (before 30 years) did not show statistically
423 significant associations with non-psychiatric hospitalizations. In contrast, people with GAD
424 and MDD comorbidity were at an increased risk of being admitted to hospital than those
425 without MDD comorbidity. The association between GAD-MDD comorbidity and non-
426 psychiatric hospital admissions was statistically significant.

427
428 People with past-year GAD were more likely to have medical conditions; nonetheless,
429 including these covariates in the model left the association between past-year GAD and
430 hospital admissions statistically significant. It was only when MDD was introduced in the
431 model as a potential confounder that any remaining association with hospital service
432 utilization was explained away.

434 **Strengths and limitations**

435
436 There are several strengths associated with our study. We had a large, population-based
437 sample of middle- and older-aged adults and adequately adjusted for a range of possible
438 confounders. We used a structured questionnaire to assess past-year GAD according to
439 DSM-IV criteria, used large administrative health databases to examine hospital service use
440 (avoiding the self-reporting bias found in questionnaire studies), and participants were
441 followed for a long time. We had a large list of self-reported physician diagnoses of chronic
442 diseases that we used to ascertain medical histories. Despite this, the residual effect of
443 diseases not captured by our study, but that are associated with GAD may be present. Past
444 illness may have been underreported, which may have introduced measurement error and
445 further attenuated effect estimates towards the null. A negligible proportion of participants
446 may have obtained care at private facilities, which might have led to non-differential
447 misclassification. The databases used in this study also did not capture admissions to

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3 448 hospitals outside the UK. However, migration in the EPIC-Norfolk cohort is minimal and
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5 449 does not present a problem.

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7 450

8 451 We may have overadjusted our models with the inclusion of self-evaluated impairment, as
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10 452 this may be part of the expression of psychiatric illness. This can lead to attenuation of
11
12 453 effect estimates. If participants chose not to answer certain questions in the HLEQ, this
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14 454 contributed to missing data; however, to avoid biasing the findings, we retained participants
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16 455 for whom we had complete data on all covariates. Non-participation in our study also may
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18 456 have led to non-differential misclassification and further attenuation of effect estimates.

19 457

20 458 Another limitation is that we did not have data on primary care service use. Merging
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22 459 population cohorts, such as ours, with primary care service administrative databases and
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24 460 hospitalization databases would have provided a more complete picture of the burden of
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26 461 GAD on the health care system.

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29 463 This study was conducted on people ages 40 years and older and may not be generalizable
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31 464 to younger age groups. We suspect that the strength of the association between GAD-MDD
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33 465 comorbidity and non-psychiatric hospital admissions is weaker for younger populations who
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35 466 are typically healthier than older people. Although young people have a high burden of
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37 467 mental health problems[40, 44], they (especially adolescents) are less likely to have non-
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39 468 psychiatric hospitalizations than older people[45]. It could take many years until the effects
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41 469 of anxiety comorbid with depression accumulate and manifest as poor physical health, thus
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43 470 translating into higher use of non-psychiatric hospital services. As such, we would expect
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45 471 the strength of the association between GAD-MDD comorbidity and hospitalizations to be
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47 472 weaker in young people, however, future studies should investigate this.

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49 474 Participants were required to complete detailed dietary and lifestyle questionnaires and
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51 475 undergo periodic health assessments. Because those who participated in EPIC-Norfolk were
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53 476 more affluent and healthier than individuals living in other parts of England, our results may
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55 477 not generalize to people living in extremely deprived areas.

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3 479 Finally, there was missing data in this study. When we conducted multiple imputations for
4 480 missing data, the effect estimate of our main analysis remained unchanged.
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8 482 **Comparison with other studies**

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11 484 Most of the studies assessing the link between psychiatric disorders and non-psychiatric
12 485 health service utilization have focused on depression and, to a lesser extent, panic disorder
13 486 and PTSD, while other anxiety disorders have been significantly underresearched. Most of
14 487 the studies on depression as a stand alone measure have shown an association with health
15 488 service use in both clinical and community samples.[46] There are substantially fewer
16 489 studies on anxiety, and a number of these have shown positive associations with health
17 490 service use. A US study[47] that recruited patients from an outpatient clinic showed that
18 491 anxiety disorders were linked to higher utilization of primary care services compared to
19 492 depressive or addictive disorders. Patients, however, were recruited from an outpatient
20 493 clinic located in a predominantly rural area, which might have affected generalizability.
21 494 Another study showed anxiety disorders to be associated with a higher number of
22 495 consultations in general medical, emergency and specialty settings, such as cardiology and
23 496 dermatology.[48] In this study, people were sampled from an anxiety clinic, thereby leading
24 497 to possible selection bias. Other studies showed PTSD and GAD to be associated with health
25 498 care use, however, this research was based on highly-select samples that have limited
26 499 generalizability.[26, 28, 49, 50] In contrast to the literature, a major strength of our study
27 500 was that it was population-based. There is also a lack of research assessing whether
28 501 different forms of the disorder contribute to even higher health service use rates (comorbid
29 502 cases are typically the most severe, hardest to treat and with the poorest prognosis [9]).
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46 504 **Mechanisms**

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50 506 A more severe course of GAD can lead to higher rates of health services because of
51 507 unhealthy behaviours, such as smoking and alcohol (which we controlled for in our
52 508 analyses). It could also be that a more severe form of anxiety, such as GAD-MDD
53 509 comorbidity is associated with poorer underlying health, which then leads to higher health
54 510 service use rates. Although we controlled for several chronic diseases, we might have
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3 511 missed some conditions that are associated with GAD-MDD comorbidity and
4 512 hospitalizations. A third explanation for higher health service use in those with comorbid
5 513 anxiety and depression could relate to inflammatory pathways. If clinically apparent signs of
6 514 disease have not yet developed in those with psychiatric comorbidity or are at an early,
7 515 undetectable stage, it will not be possible to measure these factors and adjust for them in
8 516 analyses.
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14 518 **Implications**

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16 520 GAD is a debilitating and impairing condition.[9] The evidence base on its association with
17 521 health services is small and confined to clinical settings with the potential for self-selection
18 522 bias. Our study overcomes many limitations of previous studies, and clarifies that individual
19 523 episodes of GAD measured at a single point in time (ex. in the past year) are not associated
20 524 with health service use. Instead, it shows that cases that are comorbid with depression can
21 525 lead to increased use of hospital services, after controlling for a range of important
22 526 confounders. In this study, GAD-MDD comorbidity was associated with a statistically
23 527 significantly increased risk of hospital admissions.
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34 529 Population-based research on anxiety is lacking, and thus far, no studies have assessed the
35 530 association between GAD and non-psychiatric hospitalization. Clinicians should consider
36 531 that it is not just the diagnosis of the individual disorder at one point in time (ex. past-year
37 532 GAD) that is predictive of deleterious health outcomes; different forms of the disorder may
38 533 also be important. GAD has a waxing and waning course throughout a patient's life, and
39 534 many of those affected experience relapse after psychiatric treatment or develop
40 535 psychiatric comorbidities.
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50 537 Our findings are important for clinicians and policy-makers. Large numbers of people are
51 538 affected by anxiety-depression comorbidity [9]. As such, clinicians should consider more
52 539 widespread screening for mental health problems and if appropriate, the examination of
53 540 any underlying health conditions that may require treatment in order to prevent future
54 541 hospital admissions. Policy-makers should also consider rolling out more widespread
55 542 anxiety and depression prevention and screening programmes.
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4 544 Future research, however needs to examine the reasons for the increased non-psychiatric
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6 545 hospital service use in those with GAD-MDD comorbidity (this can provide additional insight
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8 546 into clinical recommendations). To provide a better understanding of the links between
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10 547 mental and physical health, the bidirectional links between anxiety and physical health
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12 548 problems should also be examined. Finally, future research should merge a population-
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14 549 based cohort with primary and secondary care administrative health databases to provide a
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16 550 more complete picture of the burden of different forms of anxiety on the health care
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18 551 system.

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20
21 553 **Conclusion**

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24 555 People with GAD that was comorbid with MDD had a higher risk for hospital admissions
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26 556 over 9 years between 1996-1999/00 and 2009 in the European Prospective Investigation of
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28 557 Cancer in Norfolk study.

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42 580 Transparency declaration: OR affirms that the manuscript is an honest, accurate, and
43 581 transparent account of the study being reported; that no important aspects of the study
44 582 have been omitted; and that any discrepancies from the study as planned have been
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3 589 Ethical approval: The study has ethics committee approval from Norfolk Ethics Committee
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5 590 (Rec Ref: 98CN01) and all participants gave informed consent.

6
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8
9 592 corresponding author. Please contact O Remes at or260@medschl.cam.ac.uk for questions
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11 593 about the statistical code.

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49 761 understanding the relationship between PTSD, physical health, and healthcare
50 762 utilization in women veterans. *J Trauma Stress*. 2013;26:772–5 doi:
51 763 10.1002/jts.21859 [published Online First 6 November 2013].
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3 765 **Figure 1 – Flowchart of EPIC-Norfolk cohort**

4 766 This is a flowchart showing the number of participants at each study stage: the number
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6 767 approached to participate in the EPIC-Norfolk study, the number enrolled at baseline, and
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8 768 with complete data on all covariates. The EPIC-Norfolk study consists of middle-aged and
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10 769 older British people.

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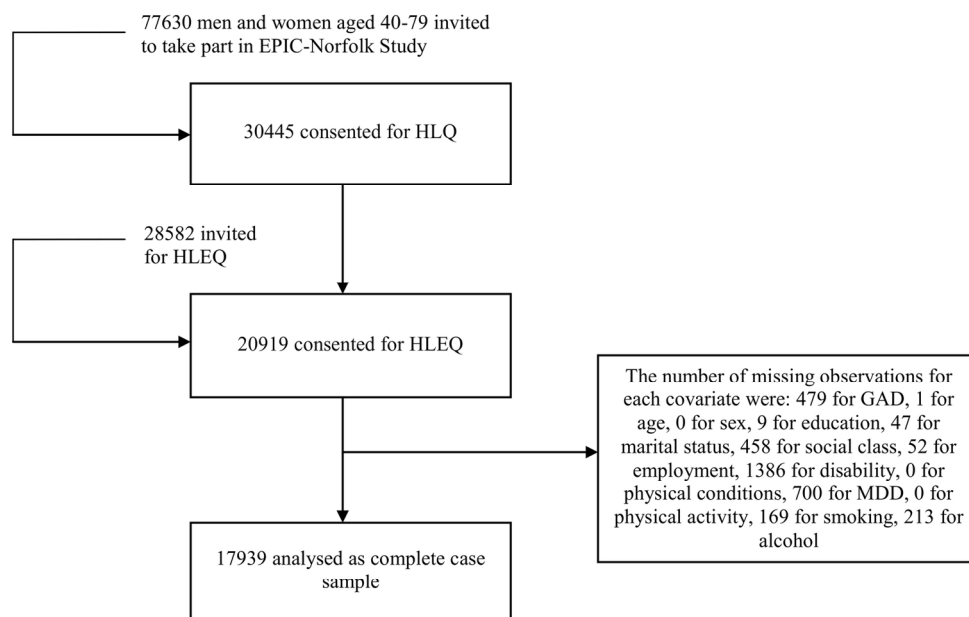
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Figure 1 - Flowchart of EPIC-Norfolk cohort



Note: Some participants had missing observations on more than one covariate.

Flowchart of the European Prospective Investigation of Cancer (EPIC)-Norfolk cohort. This is a flowchart showing the number of participants at each study stage: the number approached to participate in the EPIC-Norfolk study, the number enrolled at baseline, and with complete data on all covariates. The EPIC-Norfolk study consists of middle-aged and older British people.

153x135mm (300 x 300 DPI)

Appendix I: Table 1 Percentage and number of people with missing past-year GAD reported in 1996-2000 according to sociodemographic factors, health status, and behaviour risk factors for the EPIC-Norfolk cohort

Characteristic	Total number with characteristic	Percentage and no. with missing past-year GAD
Socio-demographics		
Age (years)		
<50	2385	1.1 (26)
50-60	6279	1.1 (70)
60-70	5787	0.9 (54)
70+	3685	1.3 (47)
Sex		
Women	10055	1.2 (118)
Men	8081	1.0 (79)
Education[†]		
Low	6178	1.2 (72)
High	11958	1.1 (125)
Marital status		
Single	695	1.3 (9)
Married	14687	1.0 (149)
Other*	2754	1.4 (39)
Social class		
Manual	6918	1.2 (82)
Non-manual	11218	1.0 (115)
Employment		
Yes	7775	0.8 (63) ^b
No	10361	1.3 (134)
Health status		
Physical conditions⁺		
Yes	9285	1.3 (119) ^b
No	8851	0.9 (78)
Disability level		
High [¶]	9030	1.4 (130) ^a
Low	9106	0.7 (67)
Psychiatric conditions		
Past-year MDD		
Yes	983	5.0 (49) ^a
No	17153	0.9 (148)
Behaviour risk factors		
Physical activity		
Active [‡]	12963	1.1 (141)
Inactive	5173	1.1 (56)
Smoking status		
Current smoker	1922	1.5 (29)
Former smoker	7543	1.0 (73)

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3	Never smoker	8671	1.1 (95)
4	Alcohol intake		
5	High ^a	9327	0.9 (86) ^b
6	Low	8809	1.3 (111)
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8			

9 ‡ High education: O-level, A-level, degree; low education: refers to no education

10 * Other: divorced, separated, widowed

11 + Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart
12 attack, cancer, diabetes, thyroid conditions, arthritis

13 ¶ Below the median PCS value of 50.6

14 ¥ Moderately inactive, moderately active, active

15 ^a 3+ units of alc./week (1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit)

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17 ^a $P < 0.001$

18 ^b $P < 0.05$

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Appendix 2 – Multiple imputations for missing data

1. Main analysis: association between past-year GAD and non-psychiatric hospital admissions

First, we imputed missing data for all covariates except GAD, our main exposure. Based on the literature, we identified potential auxiliary variables, and we retained those that were correlated with the variables in our model and were good predictors of the missing status (based on statistical tests). Our imputation model included all variables from the analysis model and the auxiliary variables.

To retain as much information as possible, we conducted the imputations on non-transformed data—the original variables in our dataset. We imputed data using the fully conditional specification, and specified a linear regression model for continuous data that were normally distributed; predictive mean matching for continuous data that were not normally distributed; and logistic regression for categorical variables. Variable estimates were subsequently averaged from 100 imputed datasets using Rubin's rules (we transformed the data before running the analytic model of interest within each of the imputed datasets).¹

We checked whether the imputations were acceptable by comparing 1) the means, standard deviations, and plots of recorded and imputed values for continuous variables, and 2) the frequencies and percentages of recorded and imputed values for each level of categorical variables.

Analyses were done using SAS 9.3 and p-values less than 0.05 were considered statistically significant.

Findings from this set of multiple imputations for missing data analysis provided the following effect estimate relating past-year GAD and non-psychiatric hospital admissions: IRR: 1.04, 95% CI: 1.02, 1.06. The IRR of 1.04 was the same as in the complete case analysis.

The same process was repeated and we imputed missing data for all covariates and also for GAD. This was the effect estimate: IRR: 1.05, 95% CI: 1.03, 1.08.

2. Subsidiary analysis: association between GAD-MDD comorbidity and non-psychiatric hospital admissions

When different forms of GAD were considered in relation to health service use, the effect estimate for GAD-MDD comorbidity was the only one that emerged as statistically significant in the complete case analysis. Therefore, we repeated this analysis using multiple imputations for missing data (similar process to that described in the first instance – we imputed missing data for all covariates except for GAD and MDD) and obtained the following result: IRR=1.20, 95% CI: 1.18, 1.22. The IRR is very similar to that obtained in the complete case analysis.

Auxiliary variables used in the imputation models

Variable	Questionnaire	Description of variable
Sociodemographic factors		
History of psychiatric illness	Health and Lifestyle Questionnaire (HLQ)	Self-reported history of other psychiatric illness
History of back pain	Health and Lifestyle Questionnaire (HLQ)	Self-reported history of back pain
History of cholesterol	Health and Lifestyle Questionnaire (HLQ)	Self-reported history of cholesterol
History of migraine	Health and Lifestyle Questionnaire (HLQ)	Self-reported history of migraine
History of tumour	Health and Lifestyle Questionnaire (HLQ)	Self-reported history of tumour

The questionnaire used for these variables have been previously described in the methods.

References

1. Berglund P, Heeringa S. Multiple imputation of missing data using SAS. Cary, NC: SAS Institute Inc, 2014.

Please see the article line numbers (column on the right) and the explanations provided.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Line numbers within the article
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	9, 44
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	35-68
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	94-141
Objectives	3	State specific objectives, including any prespecified hypotheses	143-147
Methods			
Study design	4	Present key elements of study design early in the paper	155
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	154-165, 227-228
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	154-157, 159-161, 163-165, and especially 167-169
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Outcome: 222-245 Exposure: 171-181 Confounders: 182-220
Data sources/	8*	For each variable of interest, give sources of data and details of methods of	There were two variables of interest in this study:

measurement		assessment (measurement). Describe comparability of assessment methods if there is more than one group	health service use and generalized anxiety disorder (222-248, 171-181). The others are potential confounders – in the methods I list them all, indicate how they were assessed and mention that they were collected through the baseline, self-reported postal HLQ questionnaire.
Bias	9	Describe any efforts to address potential sources of bias	I conducted a complete case analysis, followed by multiple imputations of missing data.
Study size	10	Explain how the study size was arrived at	280-282
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	How the variables were handled in analyses: 252-278 I mention that these groupings were based on the literature and provide the relevant citations. How the outcome variable was created: 224-245 How GAD was created: 173-181 Covariates: 184-220; I mention that the final categorization of the variables was also done in accordance with previous literature and I cite the relevant studies.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was	250-278 There were no subgroups or interactions examined. In addition to the main question (if past-year GAD leads to higher health service use), we also determined whether GAD frequency, chronicity, age at onset, and comorbidity with MDD are associated with health service use – this is explained in lines 271-278. We did a complete-case analysis followed by multiple imputations for missing data. Loss to follow-up was not a problem in this study. We were able to track down all participants using

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4 addressed

5 *Cross-sectional study*—If applicable, describe analytical methods taking account of
6 sampling strategy
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various means, unless they expressed that they wished
to be removed from the mailing list. We elaborate on
this in the manuscript.

8 (e) Describe any sensitivity analyses
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For peer review only

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	We do not have the reasons for non-participation, because these data were not collected when the study was initiated in 1993.
		(c) Consider use of a flow diagram	Flow diagram included in submission – figure 1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	301-302, 320-324, 341-344, as well as, tables 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	See flow diagram.
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	298-299
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	Table 2 provides the mean number of hospital admissions for those with/without GAD over the 9-year follow-up.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 3 and 4 contain unadjusted and progressively adjusted estimates. We also discussed the findings within the text, and provide odds ratios and 95% confidence intervals. We included the confounders based on the literature – we mention this in the paper and cite relevant literature. As per strobe, we included this information in the methods section; and we omitted repeating this in the results section to reduce redundancy. However, if the editor would like us to repeat this information in the results, we are happy to do so.

		(b) Report category boundaries when continuous variables were categorized	The cut-offs for age, alcohol intake, and disability levels are provided (see also footnotes of tables).
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	The Results section contains the findings from the multiple imputations for missing data analysis – we also included further information on this in an appendix. Findings for GAD frequency, chronicity, age of onset, and comorbidity with MDD are reported in table 4.
Discussion			
Key results	18	Summarise key results with reference to study objectives	415-423
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	439-477
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	514-546 (We also have a section comparing our study results to those of others: 479-499, as well as a section on potential mechanisms explaining our findings: 501-512)
Generalisability	21	Discuss the generalisability (external validity) of the study results	472-474, 460-469
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	562-563, 579-581

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.