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The association between area deprivation and major depressive disorder in British men and women: large, population study

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Article Summary

Strengths and limitations of this study

- We used a population-based sample of over 20,000 British adults and controlled for important confounders, including social class, medical history, and disability.
- We used a structured questionnaire to determine whether participants met criteria for MDD according to the DSM.
- We used the Townsend index to assess area deprivation. This index is commonly-used by . researchers to examine deprivation and is a theoretically sound measure.
- People who took part in EPIC-Norfolk were generally more affluent and healthier than • those living in other parts of England. As such, our results may not be generalizable to the most deprived areas.

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Introduction

Depression is a common psychiatric disorder affecting approximately 350 million people around the world.[1] According to the Global Burden of Disease Study[2], major depressive disorder (MDD) contributed to 689.9 per 100,000 disability-adjusted life years in men and 1161.2 per 100,000 disability-adjusted life years in women in 2010. Depression can increase the risk for impairment, disability and suicide.[3, 4, 5] It has also been linked to decreased work productivity, poor quality of life, and high health service use.[3, 6, 7]

A number of studies have examined the individual-level risk factors of depression, such as, personal and parental history of psychopathology[8], genetics[9], history of trauma and stressful life events[10, 11], and socioeconomic status.[12] However, the environment or living context can have a profound influence on mental health, over and above individual-level factors.[13, 14, 15] In a systematic review[16] of 14 studies, about half found an association between neighbourhood socioeconomic conditions and depression. Living in an area of low socioeconomic status can expose people to a higher number of stressors, such as, violence, disorder, and noise pollution, and this can have deleterious effects on mental health.[17]

There is a wealth of literature on the effect of the places where people live on mental health. Findings from systematic reviews[18, 19, 20] assessing neighbourhood characteristics and depression show that there is large heterogeneity in findings, because of differences in study populations, the confounders that are adjusted for in analyses, and the measures and definitions used to delineate neighbourhoods.[19] Although there is much evidence on the influence of area-level disadvantage or deprivation on depression, research on this relationship from a gendered perspective is lacking.

In this large, population-based, cohort study, we examine the association between area deprivation and major depressive disorder in men and women separately, while controlling for a range of important confounders, including social class, previous medical conditions, psychiatric co-morbidity, and disability. Area deprivation refers to residential environments or living contexts characterized by factors, such as, high levels of unemployment, non-home

Page 5 of 41

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ownership, non-car ownership, and low income.[13] Findings are disaggregated by sex, and
this is done for several reasons. Gender frames access to resources derived from the
environment.[21, 22] Compared to men, women have been shown to have less access to
material and social conditions, and this can influence mental health.

However, there are additional reasons why findings are disaggregated by sex. Women and men tend to react to different kinds of stressors. Recent research has shown that men are more susceptible to work- and finance-related stressors, while women are more affected by deficiencies in their social networks and interpersonal relationships. [23, 24] Hence, living in a deprived area with high levels of unemployment might be particularly detrimental for men's mental health. This was evident when the economy shifted in the UK from a manufacturing-to a service-based one, and many men lost their jobs. [25] Prior to the shift, the local economy had relied on skilled and semi-skilled jobs, typically performed by men. When the economy changed, an increasing number of women entered employment (occupying mainly service industry jobs), and this had implications for traditional sex-defined social roles. Men who experienced reduced economic opportunities may have suffered from loss of role identify and self-esteem, and this had consequences for their physical and mental health.[25] A recent study[23] showed that men's mental health is particularly affected if they fail at key instrumental tasks, such as, work achievements and ability to provide for the family. In contrast, women are more likely to be depressed if they fail to meet their needs for relationship.[23] To this end, it appears that men and women are susceptible to different kinds of stressors.

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140 It remains unclear whether men and women living in deprived areas are differentially 141 susceptible to MDD – the objective of this study will be to assess this. Knowing that one sex 142 is at risk of developing depression when exposed to deprived circumstances helps to tailor 143 interventions and allocate scarce resources according to need.[26] This is particularly 144 important at a time of scarce economic and health-related resources.

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2 3 4	146	Methods
5 6	147	
7 8	148	Data were drawn from EPIC-Norfolk, whose design and study methods have been described
9	149	in detail elsewhere.[27] In brief, a prospective population-based cohort of 30,445 participants
10 11	150	ages 40 to 74 years were recruited by post between 1993 and 1997 through general practice
12 13	151	age-sex registers in the city of Norwich and the surrounding small towns and rural areas. At
14 15	152	baseline (1993-97), participants completed a postal HLQ questionnaire that captured
16 17 18 19	153	information on sociodemographics, including age, sex, highest educational attainment,
	154	marital status, social class, and self-reported physician diagnoses of physical diseases. Using
20	155	participants' postal codes, a measure of area deprivation was derived based on the 1991
21 22	156	Census. Between 1993 and 2000, participants completed self-reported postal questionnaires
23 24 25 26 27 28 29 30 31 32 33 34 35 36 37	157	provided they: 1) were still alive, 2) did not ask to be removed from the study's mailing list,
	158	and 3) had a valid mailing address.
	159	
	160	During 1996-2000, 20,919 participants completed a structured, psychosocial Health and Life
	161	Experiences (HLEQ) questionnaire. During this time, an assessment of generalized anxiety
	162	disorder (GAD) and major depressive disorder (MDD) was made according to the Diagnostic
	163	and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[28]. Using the HLEQ
	164	questionnaire, disability measures based on the SF-36 were also derived.[29]
38 39	165	
40 41	166	All participants recruited through general-practice registers and who completed a baseline
42 43	167	health questionnaire were eligible to be included in our study; those who completed a
44	168	psychosocial questionnaire during follow-up were eligible to be included in our analysis.
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3 4 5 6 7 8 9 10 11 12 13 14 15	170	Dependent variable
	171	The primary outcome in this study was current MDD, which was measured using the HLEQ, a
	172	structured self-assessment instrument designed to provide a measure of depression for
	173	inclusion in a large-scale epidemiology project.[30, 31] DSM-IV criteria were applied to the
	174	psychiatric symptoms to determine whether participants had an episode of MDD that was
	175	ongoing at the time of the completion of the HLEQ questionnaire. Participants who reported
	176	a psychiatric episode were asked to estimate the onset and offset timings of the episode, and
16	177	then to report an outline of the history of the problem. Participants were also asked about
17 18	178	age at first symptom onset and subsequent episode recurrence.
19 20	179	
21 22	180	The dependent variable in this study is current MDD, defined as an episode of MDD reported
23 24	181	as ongoing at the time of the completion of the HLEQ.
25 26	182	
27 28	183	The following two core criteria of MDD were first evaluated:
29	184	
30 31 32 33 34 35	185	1. Have there ever been times in your life when you felt sad or depressed for two weeks or
	186	more in a row?
	187	2. Have there ever been times in your life when you lost interest in most things like your work
36 37	188	or activities that usually give you pleasure, for two weeks or more in a row?
38	189	
39 40	190	If participants answered yes to one of these questions, they were then asked to think of the
41 42	191	most recent two-week episode during their lives when these feelings of sadness, depression
43 44	192	or loss of interest were the worst. They then had to report that these feelings of being sad,
45 46	193	depressed, or loss of interest lasted all day or most of the day, and that during these two
47 48 49 50 51	194	weeks of their most recent episode, they felt this way every day or almost every day.
	195	
	196	In addition, at least five of the following symptoms had to be present: gaining or losing weight,
52 53	197	having trouble falling asleep or sleeping too much, feeling tired or low on energy, feeling
54 55	198	unable to sit still or feeling slowed down, experiencing guilt or shame, feeling worthless, losing
56 57	199	confidence, having trouble concentrating, and thinking a lot about death or suicide. One of
58 59	200	these five symptoms had to be one of the two core criteria evaluated at the beginning.
60	201	

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Finally, it was evaluated whether these symptoms interfered with participants' lives andresulted in disability or impairment.

205 Individual-level measures (potential confounders)

Individual-level measures included age, education, marital status, social class, and prevalent physical disease. The final categorization of the variables took cell size into account and was also done in accordance with previous literature.[31-37] Educational attainment was categorized into high (vocational or formal qualifications at the A- or O-level or degree-level qualifications) vs. low (no formal qualifications). Marital status was categorized into three groups: married, single (or never married), and others (widowed, divorced, separated). Social class was derived using the Computer-Assisted Standard Occupational Coding[38] and categorized as follows: I (professionals), II (managerial and technical occupations), III non-manual and III manual (skilled workers), IV (partly skilled workers), and V (unskilled manual workers). To assign social class to men and women, the male partner's current or past occupation was used. If this information was not available, the female partner's occupation was used. If the social class from either partner was unavailable, then it was coded as missing. The final categorization of social class included manual: skilled manual, partly skilled, and unskilled; and non-manual: professionals, managerial and technical, and skilled non-manual. Individual-level health status was assessed through the construction of a variable capturing major prevalent physical diseases. This was based on HLQ questions asking participants: "Has the doctor ever told you that you have any of the following?", followed by a list of options, such as allergies, asthma, cancer, stroke, heart attack, diabetes, thyroid conditions, etc.

Lifetime history of GAD was also assessed using the self-reported HLEQ questionnaire.[31] Lifetime GAD consisted of having ever had at least one episode that met core criteria stipulated by the DSM-IV. Anxiety was identified 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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To determine disability levels, we used the PCS derived from the HLEQ. The PCS is part of the SF-36, a widely-used, validated self-assessment tool. Higher scores indicate better health.[29] PCS scores were dichotomized above and below the median.

All of these individual-level variables were regarded as potential confounders and selected based on the literature and their association with depression and area-level socioeconomic circumstances.

Area-level measure (exposure variable)

To examine area deprivation, we used one of the most commonly-used measures of area deprivation in the UK: the Townsend Index.[39, 40] This index is a composite measure of four variables obtained from the 1991 Census: 1) percentage of economically active residents over age 16 who are unemployed, 2) percentage of households that do not possess a car, 3) percentage of private households that are not owner occupied, and 4) percentage of private households that are overcrowded (have more than 1 person per room). These variables were obtained at the level of the enumeration district. Each variable was standardized by obtaining Z scores (dividing the mean by the standard deviation across enumeration districts in England). The Z values of the four variables were added together to produce a Townsend index score for each enumeration district. Positive values of the index indicate enumeration districts that are more deprived, while negative values indicate those that are less deprived; 0 represents the national mean. The postal codes of participants were record linked to enumeration districts, and participants were considered to live in deprived areas depending on the Townsend index score assigned to their enumeration district.[39]

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The Townsend deprivation index was also disaggregated into its four constituent components to determine whether any one of these is associated with MDD or if it is the effect of the combined components that is important.

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Statistical analysis

Characteristics of the participants were compared by GAD status. We used correlated data analysis to assess the association between individual- and area-level risk factors of GAD. A population-average model was constructed, which accounted for the potential correlation introduced by the clustering of individuals within enumeration districts. To estimate the population-average effect of the risk factors of interest on past-year GAD, we used generalized estimating equations. As past-year GAD represents a binary outcome (yes/no) and the intra-cluster correlation is assumed to be equal, GEE with a logit link and an exchangeable correlation structure was used. Adjusted odds ratios (OR) and 95% confidence intervals based on robust standard errors were estimated. Standard multivariate logistic regression was also conducted and compared to the findings based on GEE.

Individual-level measures consisted of demographic and socio-economic status variables, whereas the area-level measure comprised the Townsend index. Townsend index scores were used to create a dichotomous variable, with 0 as the cut-point (representing the national average). Similarly, when the Townsend index was disaggregated into its four consistent components, each variable was dichotomized using 0 (the national average) as the cut-point.

Analyses were conducted separately for men and women. First, unadjusted effect estimates were determined. Next, models were constructed that adjusted for 1) age, educational attainment, marital status, and social class; then for 2) age, educational attainment, marital status, social class, and GAD; and finally for 3) age, educational attainment, marital status, social class, GAD, physical diseases and disability level. Age was first assessed as a categorical variable, and subsequently divided into 10-year bands. Models were constructed for participants with complete measurements on all covariates. It was not possible to group the GAD variable otherwise since it was created and categorized according to the DSM-IV[30, 31], and area deprivation was analysed in accordance with the literature[35, 39].

In a subsequent analysis, a fully-adjusted model was built in which the Townsend index was replaced by its four constituent components to determine whether any one of these four variables is significantly associated with GAD.

Page 11 of 41

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3 4	294	Finally, analyses were run with pure MDD as the outcome in which past-year GAD was
5 6	295	excluded. All models used two-sided statistical tests and a p-value of <0.05 was considered
7	296	statistically significant. Analyses were implemented in Statistical Analysis Software (SAS)
8 9	297	Version 9.3 (SAS Institute, Cary, NC).
10 11	298	
12 13	299	To arrive at the study size, we went through the following steps: of the 30,445 who completed
14 15	300	the baseline HLQ, we retained those participants who completed the HLEQ (20,921), and of
16	301	these, we kept those people with complete data on all covariates (18,584).
17 18	302	
19 20	303	Patient involvement
21 22	304	There were no patients involved in the development of the research question and outcome
23 24	305	measures, the design of the study, or the recruitment to and conduct of the study.
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35 36		measures, the design of the study, or the recruitment to and conduct of the study.
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3 4	308	Results
5 6	309	
7 8	310	At baseline, 30,445 participants were recruited from general practices in the city of Norwich
9 10	311	and the surrounding towns and rural areas. Of these, 20,919 people completed the HLEQ
11	312	during the follow-up period. In total, 18,582 out of 20,919 (88.8%) people were available for
12 13	313	analysis, because they had complete data on all covariates. The number of missing
14 15	314	observations for each covariate were: 9 for education, 47 for marital status, 417 for MDD, 434
16 17	315	for GAD, 458 for social class, 75 for the Townsend index, and 1386 for the SF-36. Participants
18 19	316	in this study were followed between 1993 and 2000 for a total of 7 years.
20 21	317	
22 23	318	In this sample, there were 8,239 men and 10,343 women over the age of 40 years. Table 1
23 24 25	319	shows the distribution of individual- and area-level characteristics by current MDD.
26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60		

320 Table 1: Distribution of characteristics for women (n=10,343) and men (n=8,239) who

321 completed the HLEQ questionnaire in the EPIC-Norfolk cohort

	Women		Men			
Characteristic	Number with characteristic	Percentage and number with MDD	Number with characteristic	Percentage and number with MDI		
Individual-level						
variables						
Socio-demographics						
Age (years)	0					
<50	1452	5.0 (72) ^a	964	3.4 (33) ^a		
50-60	3719	3.9 (145)	2653	3.0 (80)		
60-70	3182	2.1 (68)	2744	1.5 (40)		
>70	1990	2.7 (54)	1878	1.3 (24)		
Education [‡]						
Low	4056	3.5 (141)	2365	2.2 (51)		
High	6287	3.2 (198)	5874	2.2 (126)		
Marital status						
Single	417	2.4 (10) ^a	303	3.6 (11) ^{<i>a</i>}		
Married	7757	2.7 (207)	7240	1.7 (122)		
Other [*]	2169	5.6 (122)	696	6.3 (44)		
Social class [¥]						
Manual	3833	3.3 (127)	3288	2.3 (76)		
Non-manual	6510	3.3 (212)	4951	2.0 (101)		
Health status						
Prevalent physical						
disease						
Yes+	5702	3.8 (214) ^b	3844	2.6 (100) ^b		
No	4641	2.7 (125)	4395	1.8 (77)		
Disability level						
High¶	5299	3.9 (208) ^a	4022	3.0 (119) ^a		
Low	5044	2.6 (131)	4217	1.4 (58)		
Lifetime GAD						
Yes	448	19.4 (87) ^a	255	22.4 (57) ^a		
No	9895	2.6 (252)	7984	1.5 (120)		
Area-level variable						
Townsend index						
Deprivation						
Yes (>0)	1646	4.6 (76) ^a	1242	3.6 (45) ^a		
res (>0)	1040	1.0 (7.0)	12 12			

- ⁺ High education: O-level, A-level, degree; low education: refers to no education
 - * Other: divorced, separated, widowed
 - * Prevalent physical disease: respiratory disease (asthma and bronchitis), allergies (allergies and hay fever),
- stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis
- ^{*} Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual
- Below the median PCS value of 50.6
- $^{a}P < 0.001$ ^b P < 0.05

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The prevalence of (current) MDD was 2.1% (177/8239) for men and 3.3% (339/10343) for women. Women with MDD were younger than 50 years of age, more likely to be single, have prevalent physical disease, high disability, GAD, and live in deprived areas. Among men, similar patterns emerged (table 1).

After performing correlated data analysis, findings showed that the risk of depression in men living in the most deprived areas was 68% higher than in those living in the least deprived areas, even after accounting for age and socio-economic status (OR=1.68, 95% CI: 1.18, 2.40; to occurrence on the second p=0.004) (table 2). 🧹

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340 Table 2: Odds ratios for MDD according to individual- and area-level characteristics for

341 men (n=8,239) who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

Characteristic*	Unadjusted	Model A ¹	Model B ²	Model C ³	P-value fo Model C
Individual-level					
variables					
Socio-					
demographics					
Age					
(per 10 years)	0.65 (0.55, 0.77)	0.63 (0.53, 0.74)	0.69 (0.58, 0.82)	0.61 (0.51, 0.73)	<0.0001
Education [‡]					
Low	1.01 (0.72, 1.40)	1.11 (0.76, 1.60)	1.07 (0.73, 1.55)	1.00 (0.69, 1.46)	0.996
High	1.00	1.00	1.00	1.00	
Marital status					
Single	2.20 (1.17, 4.12)	1.87 (0.99, 3.55)	1.64 (0.86, 3.12)	1.62 (0.84, 3.14)	<0.0001
Married	1.00	1.00	1.00	1.00	
Other [*]	3.94 (2.76, 5.61)	3.97 (2.77, 5.71)	3.69 (2.47, 5.51)	3.82 (2.58, 5.66)	
Social class [¥]					
Manual	1.14 (0.84, 1.54)	0.99 (0.71, 1.36)	1.12 (0.80, 1.56)	1.04 (0.75, 1.45)	0.799
Non-manual	1.00	1.00	1.00	1.00	
Health status					
Lifetime GAD		C			
Yes	18.87 (13.36,		16.80 (11.64,	14.08 (9.72,	<0.0001
	26.65)		24.25)	20.39)	
No	1.00		1.00	1.00	
Prevalent					
physical disease					
Yes ⁺	1.50 (1.11, 2.02)			1.30 (0.94, 1.81)	0.117
No	1.00			1.00	
Disability level					
High [¶]	2.19 (1.59, 3.00)			2.20 (1.55, 3.12)	< 0.0001
Low	1.00			1.00	
Area-level					
variable					
Townsend					
index					
Deprivation					
Yes (>0)	1.96 (1.39, 2.76)	1.68 (1.18, 2.40)	1.66 (1.13, 2.44)	1.60 (1.09, 2.35)	0.018

344 1. Adjusted for age, SES (education, marital status, social class)

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- 3 345
 4 346
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 4 Prevalent physical disease: respiratory disease (asthmat bronchitis) a
 - ⁺ Prevalent physical disease: respiratory disease (asthma, bronchitis), allergies (allergies, hay fever), stroke,
- 6 348 heart attack, cancer, diabetes, thyroid conditions, arthritis
- 7 349 * Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual
 - 350 [‡] High education: O-level, A-level, degree; low education: refers to no education
 - 351 * Other: divorced, separated, widowed
 - 352 [¶] Above the median PCS value of 50.6353

12 354 *The brackets show the reference categories that were used for each categorical variable when it was entered

in the models - deprivation: no [ref] vs. yes; GAD: no [ref] vs. yes; education: high [ref] vs. low; marital status:
 married [ref], single, others; social class: non-manual [ref] vs. manual; lifetime MDD: no [ref] vs. yes; prevalent

15 357 physical disease: no [ref] vs. yes; disability level: low [ref] vs. high. These reference categories were based on 16 258 the literature. Chaosing other groupings for the netential confounder would not have abarred the results.

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358 the literature. Choosing other groupings for the potential confounders would not have changed the results.
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The OR reduced slightly after controlling for lifetime GAD (OR=1.66, 95% CI: 1.13, 2.44; p=0.009), but remained highly significant. After additionally adjusting for prevalent physical diseases and disability, the effect estimate became somewhat attenuated (OR=1.60, 95% CI: 1.09, 2.35; p=0.018), however, a strong association between area derivation and depression remained. (table 2) To determine the aspect of deprivation that is specifically associated with depression, the Townsend index was disaggregated into its four constituent components. Results showed that the OR was highest for unemployment (OR=1.82, 95% CI: 1.19, 2.77; p=0.005), followed by non-car ownership (OR=1.23, 95% CI: 0.72, 2.09; p=0.450), and lowest for overcrowding (OR=0.94, 95% CI: 0.62, 1.44; p=0.777) and non-home ownership (OR=0.82, 95% CI: 0.50, 1.35; p=0.439). Of these, only the effect estimate for unemployment was statistically significant. Men living in area characterized by high levels of unemployment were over 80% more likely to have depression than those living in areas with low levels of unemployment. Next, we wanted to determine whether deprivation is associated with pure MDD, and thus excluded past-year GAD; the association with depression remained statistically significant (OR=1.69, 95% CI: 1.10, 2.58; p=0.016).

In women, while there was a statistically significant association in the model adjusting for age, education, marital status, and social class (OR=1.41, 95% CI: 1.08, 1.84; p=0.012), the association lost its significance in the fully-adjusted model (OR=1.25, 95%CI: 0.94, 1.66; p=0.123) (table 3).

I had similar findings when the models were run with logistic regression instead of generalised estimating equations. This suggests that the intra-class correlation is negligible (findings not shown).

384 Table 3: Odds ratios for MDD according to individual- and area-level characteristics for

385 women (n=10,343) who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

Characteristic*	Unadjusted	Model A ¹	Model B ²	Model C ³	P-v M
Individual-level variables					
Socio-					
demographics					
Age					
(per 10 years)	0.75 (0.66,0.85)	0.66 (0.58, 0.76)	0.72 (0.63, 0.83)	0.68 (0.58, 0.78)	<0.0
Education [‡]					
Low	1.11 (0.89, 1.38)	1.26 (0.99, 1.60)	1.32 (1.03, 1.69)	1.33 (1.04, 1.70)	0.02
High	1.00	1.00	1.00	1.00	
Marital status					
Single	0.90 (0.47, 1.70)	0.96 (0.50, 1.83)	0.92 (0.48, 1.78)	0.92 (0.48, 1.77)	<0.0
Married	1.00	1.00	1.00	1.00	
Other [*]	2.17 (1.73, 2.73)	2.51 (1.96, 3.21)	2.38 (1.85, 3.07)	2.34 (1.82, 3.01)	
Social class [¥]					
Manual	1.02 (0.81, 1.27)	0.96 (0.75, 1.21)	0.99 (0.77, 1.27)	0.97 (0.76, 1.24)	0.80
Non-manual	1.00	1.00	1.00	1.00	
Health status					
Lifetime GAD					
Yes	9.22 (7.07,		8.37 (6.31,	7.67 (5.76,	<0.0
	12.03)		11.09)	10.20)	
No	1.00		1.00	1.00	
Prevalent					
physical					
disease ⁺					
Yes	1.41 (1.13, 1.76)			1.27 (1.00, 1.61)	0.05
No	1.00			1.00	
Disability level					
High [¶]	1.53 (1.23, 1.91)			1.45 (1.14, 1.84)	0.00
Low	1.00			1.00	
Area-level					
variable					
Townsend					
index					
Deprivation					
Yes (>0)	1.55 (1.20, 2.02)		1.28 (0.96, 1.69)	1.25 (0.94, 1.66)	0.12
No (<=0)	1.00	1.00	1.00	1.00	

387 1. Adjusted for age, socioeconomic status (education, marital status, social class)

- 2. Adjusted for age, socioeconomic status, lifetime GAD
 - 3. Adjusted for age, socioeconomic status, lifetime GAD, physical diseases and disability
 - ^{*} High education: O-level, A-level, degree; low education: refers to no education
 - Other: divorced, separated, widowed
 - ^{*} Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual
 - * Prevalent physical disease: respiratory disease (asthma, bronchitis), allergies (allergies, hay fever), stroke,
 - heart attack, cancer, diabetes, thyroid conditions, arthritis
 - Below the median PCS value of 50.6

*The brackets show the reference categories that were used for each categorical variable when it was entered in the models - deprivation: no [ref] vs. yes; GAD: no [ref] vs. yes; education: high [ref] vs. low; marital status: married [ref], single, others; social class: non-manual [ref] vs. manual; lifetime MDD: no [ref] vs. yes; prevalent physical disease: no [ref] vs. yes; disability level: low [ref] vs. high. These reference categories were based on

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the literature. Choosing other groupings for the potential confounders would not have changed the results.

1 2		
3 4	402	Discussion
5 6	403	
7 8 9 10 11 12 13 14 15 16 17 18 19 20	404	In this analysis of data from a population-based, cohort study we show, for the first time that
	405	area deprivation is significantly associated with increased risk for major depressive disorder
	406	(MDD) in men, but not in women. The association in men persisted after accounting for
	407	characteristics measured at the level of the individual, including sociodemographics and
	408	major medical conditions. When we assessed the specific aspects of deprivation associated
	409	with depression in men, we found that living in areas characterized by a high level of
	410	unemployment contributed to a high risk of depression.
	411	
21 22	412	Potential mechanisms
23 24 25 26 27 28 29 30 31 32 33 34 35	413	The living context, as measured by a Census deprivation index, appears to have a different
	414	relationship with the mental health of men and women after adjusting for a number of
	415	potential confounders. Several reasons can account for this. First, men appear to be more
	416	sensitive to stressful events occurring in their environment compared to women, especially if
	417	the stress is relating to financial and work-related problems. [23] The reason for this is that
	418	occupational and financial success is particularly important for men's mental health. Second,
	419	when living in disadvantaged regions, the possibility of hearing about job loss from others
36 37	420	increases and this can promote anticipatory stress in those who are still working, which can
38 39	421	increase their risk of depression.[41] This is particularly problematic for men who are
40	422	perceived by their families as the main provider and head of household. In contrast, women's
41 42	423	risk of depression seems to be influenced more by the social networks they are embedded in,
43 44	424	the quality and continuity of relationships, the social support derived from neighbours and
45 46	425	communities, and marital satisfaction.[23, 24] Women are more likely to experience
47 48	426	depression as a result of unmet needs in relationships. Deficiencies in interpersonal
49 50	427	relationships in women can lead to a perception that the self is unable to meet needs for self-
51	428	worth and achievements, and this can increase their risk of poor mental health.[23] Men, on
52 53	429	the other hand, have been shown to be more prone to depression as a result of failure in key
54 55	430	instrumental tasks, including achievements at work and inability to provide for the family.[23,
56 57	431	42]
58 59 60	432	

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Unemployment, often accompanied by low social ranking, can lead to loss of self-esteem and role identity in men. This was seen in the United Kingdom after the 1970's, when the economy shifted from a manufacturing to a service-based one.[25] The shift was accompanied by a loss of skilled and semi-skilled jobs among men, while women had to enter the workforce and partake in jobs that were primarily service-based. The loss of employment opportunities among men might have contributed to a loss of role identity and self-esteem in this group.[25] However, even more than a decade later after this shift in economy, men who lost their employment and were in low social class groups showed poorer self-rated health compared to women.[43] This is also mirrored by recent research.[23] This again supports the notion that men are affected by failure at key instrumental tasks.[23] The same phenomenon occurred in rural areas of Midwestern United States after the farm crisis and related events occurred in the 1980s.[44] Rural areas held agrarian values, characterized by male provider norms and 'rugged independence'.[44] After the farm crisis hit, men were no longer able to fulfil their economic provider role, and both sexes had to take on multiple jobs to make ends meet. This shook the traditional system, and created stress and contributed to high rates of depression in men. During this time, men also showed susceptibility to a wider range of stressors compared to women.[44]

Men and women also tend to experience and manifest the effect of stress in different ways. Women living in deprived areas have been shown to be more prone to anxiety[26], while men living in disadvantage are more likely to have depression. This could be a result of evolutionary, survival functions. Women have traditionally had the responsibility of childcare and ensuring the successful survival of future generations.[45] Therefore, living in deprived circumstances can trigger the fight or flight reaction, which can increase stress in findings ways to make ends meet so that they can raise their children. In this context, anxiety might be seen as protective, ensuring the survival of future generations. This is why women also tend to be more concerned about community features that can disrupt their caregiving role and negatively impact their family, such as, lack of safe play areas for children.[45, 46] Men have traditionally had the responsibility of being the provider, and if they are not able to fulfil this role, they are more likely to become depressed and potentially commit suicide.[23, 25] This is a problem in India, where suicide rates are high among male farmers whose crops have failed.[47, 48] In the UK, men with depression are also more likely than women to commit

Page 23 of 41

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suicide. Taken together, these findings suggest that women may actually be more resilient
than men when encountering adversity. However, very little research has examined this, and
previous studies in the mental health literature have typically described women as vulnerable.
Further research on health from a gendered perspective is needed.[26]

11 469

> When exposed to the stresses and strains of deprivation, men are also more likely to develop substance abuse and this, in turn, can increase the risk for depression. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study[49] showed that total number of stressors experienced in life had a significantly stronger association with heavy drinking in men than in women. Finally, when men experience mental health issues, they are less likely to seek help than women [44].

⁵ 477 Strengths and weaknesses and future research

This study reveals that depression in men is strongly linked with area disadvantage. It has several strengths. We had a large, population-based sample of middle- and older-aged adults and adequately adjusted for a range of possible confounders. We used a structured, self-reported questionnaire to assess presence of past-year GAD, and participants were followed for a long period of time. We overcome methodological limitations of previous studies by employing a commonly-used, theoretically-sound measure of area deprivation capturing important features of the environment, such as, unemployment and non-home ownership. We also had a large list of self-reported physician diagnoses of chronic physical diseases that we used to establish medical histories. Despite this, the residual effect of diseases not captured by our study, but that are associated with GAD may be present. Past illness may have been underreported, which may have introduced measurement error and attenuated effect estimates towards the null. Participants were required to complete detailed dietary and lifestyle questionnaires and undergo periodic health assessments. Because those who participated in EPIC-Norfolk were somewhat less deprived and healthier than individuals living in other parts of England[27], our results may not generalize to people living in extremely deprived circumstances.

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; ;

Future research should assess the risk of depression not only in countries, such as, the US or
 UK where there is higher gender equality, but also in parts of the world where social roles and

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gendered norms for men and women have shown much less change over time. Countries with higher gender equality also show some of the highest rates of depression and other mental disorders in the world.[50] In Europe, the discrepancy in depression rates between men and women in highly-developed countries is greater than in less-developed countries where there is also greater gender inequality.[51] In Eastern European countries, levels of depression are similar between men and women[51], while in Western Europe, women are twice as affected as men.[52] More studies are needed to explore the influence of area sf m. countries better elucidat. deprivation on the mental health of men and women separately, and to do this in different contexts (ex. rural, urban) and countries around the world. Further, the reasons behind gender differences need to be better elucidated.

2		
3 4	508	Placing our research in context
5 6 7 8 9	509	Although other studies have shown that the places where people live have a substantial
	510	impact on health[14, 15], studies on the links between area deprivation and mental disorders
	511	from a gendered perspective are limited. A recent study[53] of over 1000 African American
10 11	512	and non-Hispanic white adults living in the US showed that men who had experienced
12 13 14 15	513	stressful life events in 1983-1986 were more likely to have depression in 2011, while this was
	514	not observed in women. This study, however, has limited generalizability, because it excluded
16	515	other ethnicities. Also, the reliability and validity of the measure of stressful life events was
17 18	516	not reported – the measure was based on a checklist of 'major negative events' that had
19 20	517	occurred in the previous 3 years. Finally, exposure to stressful life events at the individual-
21 22	518	level were investigated, rather than the effect of the place people live in.
23 24	519	
25 26	520	A number of studies have assessed individual-level risk factors of depression, but substantially
27 28	521	fewer have examined the influence of the environment on mental health. Nonetheless,
29	522	studies of individual-level risk factors provide an important starting point in understanding
30 31	523	relationships. Another prospective UK study of over 500 people[25] showed that the
32 33	524	socioeconomic status of men at midlife was associated with depression at midlife, while this
34 35	525	was not observed in women. For women, their socioeconomic status at birth influenced their
36 37	526	levels of depression at midlife. Also, men who had experienced downward social mobility or
38 39	527	a reduction in their socioeconomic status from adulthood to midlife were at high risk of having
40	528	poor mental health at midlife, but this was not found in women.[25] These results suggest
41 42	529	that women are more sensitive to the social class group they are in very early in life, while for
43 44	530	men, social mobility over the life course, as well as the socioeconomic status group they are
45 46	531	in during later life are more important for their mental health. This study, however, was
47 48	532	limited, because it was based on a small sample size, assessed only individual-level measures
49	533	rather than area-level level effects, and failed to adjust for a number of important
50 51	534	confounders, such as, demographic factors. Failure to properly adjust for potential
52 53	535	confounders can lead to overestimation of the effect estimate. Finally, this study examined
54 55	536	general mental health, rather than individual psychiatric disorders.
56 57	537	
58	538	A recent US study showed that the types of stressors that influence men's risk of depression

A recent US study showed that the types of stressors that influence men's risk of depression
 are those related to work, finances, and legal matters.[23] In this study, stressors were not

540 linked to depression risk in women. Again, this research only assessed individual-level data. 541 Our study shows, for the first time that living in a deprived area increases the risk of 542 depression in men, while less so in women. Area deprivation was measured in our study at 543 midlife and beyond, the time period which seems to have the greatest influence on men's 544 mental health.[23]

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546 Interpretation

The absolute number of people living in deprived areas across the globe is large. When this is considered along with the growing mental health burden worldwide, our findings are highly relevant. There is a need to reduce social and health inequalities, and we provide a strong evidence base in support of this. When developing mental health policy, the places where people live need to be taken into account and greater investments in relation to employment opportunities in deprived communities need to be made. We show that gender is an important factor when it comes to assessing the impact of the environment, and promoting good mental health. Our findings also suggest that financial investments made to local areas will not benefit everyone equally, and this is particularly important at a time of scarce economic- and health-related resources. Regarding clinical implications, health professionals should consider assessing depression in men living in deprived areas.

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29	573	approved the final version. The authors had full access to all the data in the study and take
30 31	574	responsibility for the integrity of the data and the accuracy of the data analysis. OR acts as
32 33	575	guarantor of the study.
34 35	575	guarantoi oi the study.
36 37	576	
38	577	Transparency declaration: OR affirms that the manuscript is an honest, accurate, and
39 40	578	transparent account of the study being reported; that no important aspects of the study have
41 42	579	been omitted; and that any discrepancies from the study as planned have been explained.
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	584	
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	587	
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	589	

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	Item No	Recommendation	r uses i	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 	6, ateg to t	er 2019. De
Introduction		06	870 data 140a	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	87 4	우
Objectives	3	State specific objectives, including any prespecified hypotheses	14 8	
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Study design	4	Present key elements of study design early in the paper		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		5 154-161
Participants	6	 (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—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 Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case 	1659-1 1659-1 Tham colfert	10, 148-151, 156-158 naguscript also mentions that the EPIC-Norfolk t was record linked to hospitalization databases we up). on June 14, 2025 at Age
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Data sources/ neasurement	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		vage on and major depressive disorder (243-256,

Page 37 of 41			BMJ Open	by copyright 17 the others are potential confounders – in
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8	Study size	10	Explain how the study size was arrived at	28 5786 29 8 30 5
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37 38 39 40 41 42 43 44 45 46			(<i>d</i>) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed For peer review only - http://bmjopen.bmj.com/site/about/guidelines.	Loss to to to track down all participants using warious means, unless they expressed that they wished

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		(b) Give reasons for non-participation at each stage	We do not have the reasons for non-participation, be the set of the study way in the study way in the study
		(c) Consider use of a flow diagram	Were deen a paper which describes the EPIC- Northelestudy further. This paper contains a flow diagram Also, our previously-published BMJ Open particulation which this one was based contains a flow diagram also – we reference this paper.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	We provided characteristics for those with vs. withou MipD, because we felt it was important to show the characteristics of those exposed vs. non-exposed (see alse Tagle 1)
		 (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i>—Summarise follow-up time (eg, average and total amount) 	31 4 -31 6 31 6
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time 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	335 D ON June
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 and 3 contain unadjusted and progressively adjusted estimates. We also discussed the findings within the text, and provide odds ratios and 95% confidence intervals (336-339, 360-383). We included the confounders based on the literature - we mergion this in the paper and cite relevant literature. As per strobe, we included this information
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Discussion	10		40 4 -41	
Key results Limitations	18 19	Summarise key results with reference to study objectives Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	48649	
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The association between area deprivation and major depressive disorder in British men and women: large, cohort study

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The association between area deprivation and major depressive disorder in British men and women: large cohort study

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Tables: 3

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ABSTRACT

OBJECTIVE

Studies have shown area-level deprivation can increase the risk for mental disorders over and above individual-level circumstances, such as education and social class. The objective of this study is to determine whether area deprivation is associated with major depressive disorder (MDD) in British women and men separately while adjusting for individual-level factors.

DESIGN

Large, population study.

SETTING

UK population-based cohort.

PARTICIPANTS

30,445 people from the general population aged 40 years and older and living in England consented to participate at study baseline, and of these, over 20,000 participants completed a structured Health and Life Experiences Questionnaire (HLEQ) used to capture MDD. Area deprivation was measured in 1991 using Census data, and current MDD was assessed in 1996-2000. 8,236 men and 10,335 women had complete data on all covariates.

PRIMARY OUTCOME MEASURE

MDD identified according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).

RESULTS

In this study, 3.3% (339/10,335) of women and 2.1% (177/8,236) of men had MDD. Men living in the most deprived areas were 51% more likely to have depression than those living in areas that were not deprived (OR=1.51, 95% CI: 1.01 to 2.24; p=0.043), but the association between deprivation and MDD was not statistically significant in women (OR=1.24, 95%CI: 0.93 to 1.65; p=0.143).

CONCLUSION

This study shows that the residential environment differentially affects men and women, and this needs to be taken into account by mental health policy-makers. Knowing that men living in deprived conditions are at high risk for having depression helps inform targeted prevention and intervention programs.

Article Summary

Strengths and limitations of this study

- We used a population-based sample of over 20,000 British adults and controlled for important confounders, including social class, medical history, and disability.
- We used a structured questionnaire (the Health and Life Experiences Questionnaire of the EPIC-Norfolk study) to determine whether participants met criteria for MDD according to the DSM.
- We used the Townsend index to assess area deprivation. This index is commonly-used by researchers to examine deprivation and is a theoretically sound measure.
- People who took part in EPIC-Norfolk were generally more affluent and healthier than those living in other parts of England. As such, our results may not be generalizable to the most deprived areas.

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Introduction

Depression is a common psychiatric disorder affecting approximately 350 million people around the world.[1] According to the Global Burden of Disease Study[2], major depressive disorder (MDD) contributed to 689.9 per 100,000 disability-adjusted life years in men and 1161.2 per 100,000 disability-adjusted life years in women in 2010. Depression can increase the risk for impairment, disability and suicide.[3, 4, 5] It has also been linked to decreased work productivity, poor quality of life, and high health service use.[3, 6, 7]

A number of studies have examined the individual-level risk factors of depression, such as, personal and parental history of psychopathology[8], genetics[9], history of trauma and stressful life events[10, 11], and socioeconomic status.[12] However, the environment or living context can have a profound influence on mental health, over and above individual-level factors.[13, 14, 15] In a systematic review[16] of 14 studies, about half found an association between neighbourhood socioeconomic conditions and depression. Living in an area of low socioeconomic status can expose people to a higher number of stressors, such as, violence, disorder, and noise pollution, and this can have deleterious effects on mental health.[17]

There is a wealth of literature on the effect of the places where people live on mental health. Findings from systematic reviews[18, 19, 20] assessing neighbourhood characteristics and depression show that there is large heterogeneity in findings, because of differences in study populations, the confounders that are adjusted for in analyses, and the measures and definitions used to delineate neighbourhoods.[19] Although there is much evidence on the influence of area-level disadvantage or deprivation on depression, research on this relationship from a gendered perspective is lacking.

In this large, population-based, cohort study, we examine the association between area deprivation and major depressive disorder in men and women separately, while controlling for a range of important confounders, including social class, previous medical conditions, psychiatric co-morbidity, and disability. Area deprivation refers to residential environments or living contexts characterized by factors, such as, high levels of unemployment, non-home

Page 5 of 49

BMJ Open

ownership, non-car ownership, and low income.[13] Findings are disaggregated by gender, and this is done for several reasons. Gender frames access to resources derived from the environment.[21, 22] Compared to men, women have been shown to have less access to material and social conditions, such as income, power, and social status, and this can influence mental health. Women have historically been the victims of discrimination, and because of this have had limited opportunities for education, and well-remunerated and respected forms of employment.[23] Women have taken on different job roles and tasks than men, which has exposed them to different hazards and contaminants affecting their health. Women have traditionally been seen as 'care-takers' in society and involved in domestic work, which might have led to an interruption in their education or career paths. As such, they have derived fewer resources with which they could maintain or improve their health.[23, 24]

However, there are additional reasons why findings are disaggregated by gender. Women and men tend to react to different kinds of stressors. Recent research has shown that men are more susceptible to work- and finance-related stressors, while women are more affected by deficiencies in their social networks and interpersonal relationships. [25, 26] This research is based on a study conducted in the US and other parts of the world. Hence, living in a deprived area with high levels of unemployment might be particularly detrimental for men's mental health. This was evident when the economy shifted in the UK from a manufacturingto a service-based one, and many men lost their jobs.[27] Prior to the shift, the local economy had relied on skilled and semi-skilled jobs, typically performed by men. When the economy changed, an increasing number of women entered employment (occupying mainly service industry jobs), and this had implications for traditional gender-defined social roles. Men who experienced reduced economic opportunities may have suffered from loss of role identify and self-esteem, and this had consequences for their physical and mental health.[27] A recent study[25] showed that men's mental health is particularly affected if they fail at key instrumental tasks, such as, work achievements and ability to provide for the family. In contrast, women are more likely to be depressed if they fail to meet their needs for relationship.[25] To this end, it appears that men and women are susceptible to different kinds of stressors.

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It remains unclear whether men and women living in areas of above average deprivation are differentially susceptible to MDD – the objective of this study will be to assess this. Knowing that one gender is at risk of developing depression when exposed to deprived circumstances helps to tailor interventions and allocate scarce resources according to need.[28] This is particularly important at a time of scarce economic and health-related resources.

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Methods

Data were drawn from EPIC-Norfolk, whose design and study methods have been described in detail elsewhere.[29] In brief, a prospective population-based cohort of 30,445 participants ages 40 to 74 years were recruited by post between 1993 and 1997 through general practice age-sex registers in the city of Norwich and the surrounding small towns and rural areas. At baseline (1993-97), participants completed a postal Health and Life Experiences (HLQ) questionnaire that captured information on sociodemographics, including age, gender, highest educational attainment, marital status, social class, employment status, ethnicity and self-reported physician diagnoses of physical diseases. Using participants' postal codes, a measure of area deprivation was derived based on the 1991 Census. Between 1993 and 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.

During 1996-2000, 20,919 participants completed a structured, psychosocial Health and Life Experiences (HLEQ) questionnaire. During this time, an assessment of generalized anxiety disorder (GAD) and major depressive disorder (MDD) was made according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[30]. Using the HLEQ questionnaire, disability measures based on the SF-36 were also derived.[31]

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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.

In regards to the study size, an initial sample of 30,445 participants completed the baseline HLQ and of these, 20,921 filled out the psychosocial HLEQ. After retaining the people with complete measures on all covariates, the final sample size was 18,571.

Although EPIC-Norfolk is a prospective study and area derivation was measured in 1991 and anxiety in 1996-2000, this analysis should be considered cross-sectional.

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Dependent variable

The primary outcome in this study was current MDD, which was measured using the HLEQ, a structured self-assessment instrument designed to provide a measure of depression for inclusion in a large-scale epidemiology project.[32, 33] DSM-IV criteria were applied to the psychiatric symptoms to determine whether participants had an episode of MDD that was ongoing at the time of the completion of the HLEQ questionnaire. Participants who reported a psychiatric episode were asked to estimate the onset and offset timings of the episode, and then to report an outline of the history of the problem. Participants were also asked about age at first symptom onset and subsequent episode recurrence.

The dependent variable in this study is current MDD, defined as an episode of MDD reported as ongoing at the time of the completion of the HLEQ.

The following two core criteria of MDD were first evaluated:

1. Have there ever been times in your life when you felt sad or depressed for two weeks or more in a row?

2. Have there ever been times in your life when you lost interest in most things like your work or activities that usually give you pleasure, for two weeks or more in a row?

If participants answered yes to one of these questions, they were then asked to think of the most recent two-week episode during their lives when these feelings of sadness, depression or loss of interest were the worst. They then had to report that these feelings of being sad, depressed, or loss of interest lasted all day or most of the day, and that during these two weeks of their most recent episode, they felt this way every day or almost every day.

In addition, at least five of the following symptoms had to be present: gaining or losing weight, having trouble falling asleep or sleeping too much, feeling tired or low on energy, feeling unable to sit still or feeling slowed down, experiencing guilt or shame, feeling worthless, losing confidence, having trouble concentrating, and thinking a lot about death or suicide. One of these five symptoms had to be one of the two core criteria evaluated at the beginning.

 Finally, it was evaluated whether these symptoms interfered with participants' lives and resulted in disability or impairment.

Individual-level measures (potential confounders)

Individual-level measures included age, education, employment status, marital status, social class, prevalent physical disease, and ethnicity. The final categorization of the variables took cell size into account and was also done in accordance with previous literature.[33-39] Age was divided into 10-year bands. Educational attainment was categorized into high (vocational or formal qualifications at the A- or O-level or degree-level qualifications) vs. low (no formal qualifications). Further details on the meaning of A- and O-level can be found elsewhere[40, 41]; the appendix also contains definitions of these (appendix 1). Employment was divided into yes vs. no. Marital status was categorized into three groups: married, single (or never married), and others (widowed, divorced, separated). Social class was derived using the Computer-Assisted Standard Occupational Coding[42] and categorized as follows: I (professionals), II (managerial and technical occupations), III non-manual and III manual (skilled workers), IV (partly skilled workers), and V (unskilled manual workers). To assign social class to men and women, the male partner's current or past occupation was used. If this information was not available, the female partner's occupation was used. If the social class from either partner was unavailable, then it was coded as missing. The final categorization of social class included manual: skilled manual, partly skilled, and unskilled; and non-manual: professionals, managerial and technical, and skilled non-manual. Individuallevel health status was assessed through the construction of a variable capturing major prevalent physical diseases. This was based on HLQ questions asking participants: "Has the doctor ever told you that you have any of the following?", followed by a list of options, such as allergies, asthma, cancer, stroke, heart attack, diabetes, thyroid conditions, etc. Ethnicity was based on a self-reported question asking participants to tick the relevant box: 'white', 'black Caribbean', 'black other', 'Indian', 'Pakistani', 'Bangladeshi', 'Chinese', 'other'.

Lifetime history of GAD was also assessed using the self-reported HLEQ questionnaire.[33] Lifetime GAD consisted of having ever had at least one episode that met core criteria stipulated by the DSM-IV. Anxiety was identified if participants reported having uncontrollable, excessive worry for six months or longer on most days than not that resulted

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> 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.

> To determine disability levels, we used the physical component summary (PCS) derived from the HLEQ. The PCS is part of the SF-36, a widely-used, validated self-assessment tool. The SF-36 is a 36-item measure capturing 8 health dimensions: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy/vitality, bodily pain, and general health perception. The eight dimensions of the SF-36 were used to create two higher order scores, one of which was the PCS. Higher scores indicate better health.[31] PCS scores were dichotomized above and below the median.

> All of these individual-level variables were regarded as potential confounders and selected based on the literature and their association with depression and area-level socioeconomic circumstances.

Area-level measure (exposure variable)

To examine area deprivation, we used the Townsend Index.[43, 44] This is one of the most commonly-used measures of area deprivation in the UK and particularly appropriate for the time of the original EPIC-Norfolk study. This index is a composite measure of four variables obtained from the 1991 Census: 1) percentage of economically active residents over age 16 who are unemployed, 2) percentage of households that do not possess a car, 3) percentage of private households that are not owner occupied, and 4) percentage of private households that are overcrowded (have more than 1 person per room). These variables were obtained at the level of the enumeration district, which is a geographic area used for census purposes in Britain. Each variable was standardized by obtaining Z scores (dividing the mean by the standard deviation across enumeration districts in England). The Z values of the four variables were added together to produce a Townsend index score for each enumeration district. A score of 0 represents the national mean, while positive values of the index indicate enumeration districts that are above average deprivation, while negative values indicate

 those that are below average deprivation. The postal codes of participants were record linked to enumeration districts, and participants were considered to live in areas of above average deprivation depending on the Townsend index score assigned to their enumeration district.[43]

The Townsend deprivation index was also disaggregated into its four constituent components to determine whether any one of these is associated with MDD or if it is the effect of the combined components that is important.

Missing data

The number of missing observations for each covariate were: 9 for education, 47 for marital status, 417 for MDD, 434 for GAD, 458 for social class, 75 for the Townsend index, and 1386 for the SF-36, 52 for employment status.

Statistical analysis

First, we compared participants on sociodemographic, and medical and psychiatric history characteristics, and the prevalence of MDD was computed for sub-groups. Next, we undertook correlated data analysis based on generalized estimating equations (GEE)[45, 46] to determine the population-average effect of living in an area of above average deprivation on risk of having depression while controlling for confounders. MDD is a dichotomous outcome and the intra-cluster correlation was assumed to be equal. As such, we used GEE with a logit link and an exchangeable correlation structure.

First, we ran unadjusted analyses between deprivation and MDD. To determine the influence of potential confounders on risk of having depression, we progressively adjusted the models and accounted for 1) age, educational attainment, marital status, and social class; then for 2) age, educational attainment, marital status, social class, and GAD; and finally for 3) age, educational attainment, marital status, social class, GAD, physical diseases and disability level. We conducted separate analyses for men and women. The individual-level covariates were sociodemographics, and medical and psychiatric history, while the area-level covariate was the Townsend index score. The progressively adjusted models allowed us to estimate adjusted odds ratios (OR) and 95% confidence intervals based on robust standard errors.

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A dichotomous variable was created using the Townsend index scores, and 0 was used as the cut-point (considered to be the national average). The variable was dichotomized, because we wanted to compare participants' scores to the national average[47] - scores above the cut-point of 0 were considered above average deprivation. A binary variable was also used in accordance with previous research[47] and because of cell size considerations – we wanted to ensure that there were sufficient people with MDD in each category of the deprivation variable.

Models were constructed for participants with complete measurements on all covariates. It was not possible to group the MDD variable otherwise since it was created and categorized according to the DSM-IV[32, 33], and area deprivation was analysed in accordance with the literature[37, 43].

Several sensitivity analyses were undertaken. We ran fully-adjusted models using pure MDD as the outcome, in which those with past-year GAD were excluded. It should be mentioned that although GAD and MDD have been regarded as closely correlated by many researchers, they are independent disorders. The high GAD-MDD comorbidity found in older literature was due to the use of clinical populations with multiple co-occurring conditions.

Next, we disaggregated the index used to measure disadvantage. If a significant relationship was found between area deprivation and depression for one of the genders in a fully-adjusted model, we investigated further. We disaggregated the Townsend index into its 4 constituent components (unemployment, non-home ownership, non-car ownership, and overcrowding) to determine whether any aspect of deprivation is associated with increased risk of having depression in that gender group. Each component was dichotomized using a cut-point of 0, because it represents the national average.

Then we determined whether relationships held after dividing the Townsend index into quintiles and adjusting for sociodemographic and health status variables. Further, we examined whether the inclusion of additional covariates or recategorization of variables made any difference to the effect estimates. We included ethnicity as a potential confounder

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Finally, we conducted logistic regression, which does not take the intra-cluster correlation into account, and compared the findings to those from GEE. Similar results between the models suggests that the intraclass correlation is negligible.

All models used two-sided statistical tests, and a p-value of <0.05 was considered statistically significant. Statistical Analysis Software (SAS) Version 9.3 (SAS Institute, Cary, NC) was used in these analyses.

Patient and Public Involvement:

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

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Results

At baseline, 30,445 participants were recruited from general practices in the city of Norwich and the surrounding towns and rural areas. Of these, 20,919 people completed the HLEQ during the follow-up period. In total, 18,571 out of 20,919 (89%) people were available for analysis, because they had complete data on all covariates.

In this sample, there were 8,236 men and 10,335 women over the age of 40 years. Table 1 shows the distribution of individual- and area-level characteristics by current MDD.

Table 1: Distribution of characteristics for women and men who completed the HLEQquestionnaire in the EPIC-Norfolk cohort

	Women (n=10,335)	Men (n=8,236)			
Characteristic	Number with characteristic	Percentage and number with MDD	Number with characteristic	Percentage and number with MD		
Individual-level variables						
Socio-demographics						
Age (years)	0					
<50	1450	5.0 (72) ^a	964	3.4 (33) ^a		
50-60	3716	3.9 (145)	2651	3.0 (80)		
60-70	3180	2.1 (68)	2743	1.5 (40)		
>70	1989	2.7 (54)	1878	1.3 (24)		
Education [‡]						
Low	4050	3.5 (141)	2365	2.2 (51)		
High	6285	3.2 (198)	5871	2.1 (126)		
Marital status						
Single	417	2.4 (10) ^a	303	3.6 (11) ^a		
Married	7750	2.7 (207)	7237	1.7 (122)		
Other [*]	2168	5.6 (122)	696	6.3 (44)		
Social class [¥]						
Manual	3829	3.3 (127)	3286	2.3 (76)		
Non-manual	6506	3.3 (212)	4950	2.0 (101)		
Employment						
Yes	4075	128 (3.1)	3821	68 (1.8) ^b		
No	6260	(3.4) 211	4415	109 (2.5)		
Health status						
Prevalent physical						
disease						
Yes⁺	5698	3.8 (214) ^b	3843	2.6 (100) ^b		
No	4637	2.7 (125)	4393	1.8 (77)		
Disability level						
High [¶]	5296	3.9 (208) ^{<i>a</i>}	4021	3.0 (119) ^a		
Low	5039	2.6 (131)	4215	1.4 (58)		
Lifetime GAD						
Yes	448	19.4 (87) ^a	255	22.4 (57) ^a		
No	9887	2.5 (252)	7981	1.5 (120)		
Area-level variable						
Townsend index						

Above average deprivation (>0)	1646	4.6 (76) ^a	1242	3.6 (45) ^a
Below average	8689	3.0 (263)	6994	1.9 (132)

deprivation (<=0)

** Please see appendix 2 for the distribution of the Townsend index scores in men and women.

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

* Other: divorced, separated, widowed

* Prevalent physical disease: respiratory disease (asthma and bronchitis), allergies (allergies and hay fever),

stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

* Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual

 ¶ Below the median PCS value of 50.6

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^a P < 0.001

^b P < 0.05

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 The prevalence of (current) MDD was 2.1% (177/8236) for men and 3.3% (339/10335) for women. Women with MDD were younger than 50 years of age, more likely to be divorced/separated/widowed, have prevalent physical disease, high disability, GAD, and live in areas of above average deprivation. Among men, similar patterns emerged (table 1). Men with MDD were also more likely to be unemployed.

After performing correlated data analysis based on GEE, findings showed that the risk of of . 95% CI: . depression in men living in areas of above average deprivation was 95% higher in an unadjusted analysis (OR=1.95, 95% CI: 1.39, 2.76; p=0.0001). After accounting for sociodemoraphics, the odds ratio attenuated slightly to 1.57 (OR=1.57, 95% CI: 1.09, 2.26; p=0.0152) (table 2).

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Table 2: Odds ratios for MDD according to individual- and area-level characteristics for men (n=8,236) who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

			Odds ratios ar	nd 95% CI		
Characteristic*	Model A ¹	P-value for model A	Model B ²	P-value for model B	Model C ³	P-value for Model C
Individual-level variables						
Socio-						
demographics						
Age						
(per 10 years)	0.40 (0.32,	<0.0001	0.50 (0.40,	< 0.0001	0.47 (0.38,	<0.0001
	0.50)		0.63)		0.60)	
Education [‡]						
Low	1.10 (0.76,	0.6081	1.06 (0.72,	0.7813	1.00 (0.68,	0.9978
	1.61)		1.54)		1.46)	
High	1.00		1.00		1.00	
Marital status						
Single	1.46 (0.76,	<0.0001	1.39 (0.71,	<0.0001	1.41 (0.72,	<0.0001
	2.83)		2.68)		2.76)	
Married	1.00		1.00		1.00	
Other [*]	3.66 (2.53,		3.48 (2.31,		3.58 (2.39,	
- · · · · ·	5.28)		5.22)		5.35)	
Social class [¥]			L			
Manual	1.02 (0.73,	0.9161	1.14 (0.81,	0.4612	1.06 (0.76,	0.7298
	1.41)		1.59)		1.48)	
Non-manual	1.00		1.00		1.00	
Employment [¥]	2 60 /2 49	<0.0001	2 6 4 / 1 7 4	-0.0001	2 24 /1 46	0.0002
No	3.69 (2.48, 5.50)	<0.0001	2.64 (1.74,	<0.0001	2.24 (1.46,	0.0002
Yes	5.50)		4.03) 1.00		3.45) 1.00	
Health status			1.00		1.00	
Lifetime GAD						
Yes			14.33 (9.84,	<0.0001	12.65 (8.68,	<0.0001
			20.87)		18.44)	.0.0001
No			1.00		1.00	
Prevalent						
physical						
disease						
Yes+					1.25 (0.89 <i>,</i> 1.75)	0.1977

No					1.00	
Disability level						
High¶					1.98 (1.39,	0.0002
					2.82)	
Low					1.00	
Area-level						
variable						
Townsend						
index						
Deprivation						
Above	1.57 (1.09,	0.0152	1.56 (1.05,	0.0287	1.51 (1.01,	0.043
average	2.26)		2.31)		2.24)	
deprivation						
(>0)						
Below	1.00		1.00		1.00	
average						
deprivation						
(<=0)						

1. Adjusted for age, SES (education, marital status, social class, employment status)

2. Adjusted for age, SES, lifetime GAD

3. Adjusted for age, SES, lifetime GAD, physical diseases and disability

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

[¥] Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual

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

* Other: divorced, separated, widowed

[¶] Above the median PCS value of 50.6

*The brackets show the reference categories that were used for each categorical variable when it was entered in the models - deprivation: below average deprivation [ref] vs. above average deprivation; education: high [ref] vs. low; marital status: married [ref], single, others; social class: non-manual [ref] vs. manual; employment: yes [ref] vs. no; lifetime GAD: no [ref] vs. yes; prevalent physical disease: no [ref] vs. yes; disability level: low [ref] vs. high. These reference categories were based on the literature. Choosing other groupings for the potential confounders would not have changed the results.

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The OR reduced slightly after controlling for lifetime GAD (OR=1.56, 95% CI: 1.05, 2.31; p=0.029), but remained highly significant. After additionally adjusting for prevalent physical diseases and disability, the effect estimate became somewhat attenuated (OR=1.51, 95% CI: 1.01, 2.24; p=0.043), however, a statistically significant association between area derivation and depression remained (table 2). To determine the aspect of deprivation that is specifically linked to depression, the Townsend index was disaggregated into its four constituent components. Results showed that the OR was highest for unemployment (OR=1.77, 95% CI: 1.16, 2.71; p=0.008), followed by non-car ownership (OR=1.20, 95% CI: 0.70, 2.04; p=0.507), and lowest for overcrowding (OR=0.93, 95% CI: 0.60, 1.42; p=0.727) and non-home ownership (OR=0.81, 95% CI: 0.49, 1.34; p=0.422). Of these, only the effect estimate for unemployment was statistically significant. Men living in area characterized by high levels of unemployment were almost 80% more likely to have depression than those living in areas with low levels of unemployment. Next, we wanted to determine whether deprivation is associated with pure MDD, and thus excluded past-year GAD; the association with depression remained statistically significant (OR=1.64, 95% CI: 1.06, 2.52; p=0.025).

In women, while there was a statistically significant association in the unadjusted analysis (OR=1.55, 95% 1.19, 2.01; p=0.0010) as well as in the model adjusting for sociodemographics (OR=1.40, 95% CI: 1.07, 1.84; p=0.013), the association lost its significance in the fully-adjusted model (OR=1.24, 95%CI: 0.93, 1.65; p=0.143) (table 3).

We also conducted some sensitivity analyses. First, we divided the Townsend index into quintiles. Results showed that men living in the most deprived quintile had a statistically significantly increased risk for depression (OR=1.68, 95% CI: 1.01, 2.79; 0.0472), while none of the quintiles for women showed statistically significant findings. Second, we wanted to determine whether there was any change in findings after incorporating ethnicity in the original fully-adjusted models. The associations remained the same (men: OR=1.53, 95% CI: 1.03, 2.27 and women: OR=1.25, 95% CI: 0.94, 1.66). Second, we undertook analyses in which the education variable was left in its original form (divided into 4 categories: no education, O-level, A-level, degree and beyond) in fully-adjusted models, and similar findings were again obtained (men: OR=1.51, 95% CI: 1.02, 2.24) and women: OR= OR=1.23, 95% CI: 0.92, 1.63). Third, we re-ran the fully-adjusted models using logistic regression rather than correlated

data analysis based on GEE (Appendix 3), and results remained essentially unchanged (men: OR=1.51, 95% CI: 1.03, 2.21 and women: OR=1.24, 95% CI: 0.94, 1.64). This shows that there indeed is a robust association between area deprivation and depression in men, while there is no statistically significant effect in women.

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Table 3: Odds ratios for MDD according to individual- and area-level characteristics for women (n=10,335) who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

	Odds ratios and 95% Cl								
Characteristic*	Model A ¹	P-value for model A	Model B ²	P-value for model B	Model C ³	P-value for Model C			
Individual-level variables									
Socio- demographics									
Age (per 10 years)	0.54 (0.46, 0.64)	<0.0001	0.62 (0.52, 0.74)	<0.0001	0.59 (0.50, 0.71)	<0.0001			
Education [‡]	0.04)				0.71)				
Low	1.23 (0.97, 1.56)	0.0890	1.29 (1.01, 1.65)	0.0412	1.30 (1.02 <i>,</i> 1.66)	0.0356			
High	1.00		1.00		1.00				
Marital status									
Single	0.93 (0.48, 1.78)	<0.0001	0.91 (0.48, 1.75)	<0.0001	0.91 (0.47, 1.75)	<0.0001			
Married	1.00		1.00		1.00				
Other*	2.56 (2.00, 3.27)		2.41 (1.87, 3.10)		2.36 (1.83, 3.04)				
Social class [¥]									
Manual	0.95 (0.75 <i>,</i> 1.21)	0.6964	0.99 (0.77, 1.27)	0.9530	0.97 (0.76 <i>,</i> 1.25)	0.8225			
Non-manual	1.00		1.00		1.00				
Employment [¥]									
No	1.87 (1.42, 2.48)	<0.0001	1.62 (1.21, 2.15)	0.0010	1.55 (1.17, 2.06)	0.0026			
Yes			1.00		1.00				
Health status									
Lifetime GAD									
Yes			7.97 (5.99, 10.60)	<0.0001	7.37 (5.52, 9.83)	<0.0001			
No			1.00		1.00				
Prevalent									
physical									
disease									
Yes+					1.25 (0.98, 1.59)	0.0682			
No					1.00				

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Disability level						
High¶					1.41 (1.11,	0.004
					1.79)	
Low					1.00	
Area-level						
variable						
Townsend						
index						
Deprivation						
Above	1.40 (1.07,	0.0132	1.26 (0.95, 1.67)	0.1081	1.24 (0.93,	0.142
average	1.84)				1.65)	
deprivation						
(>0)						
Below	1.00		1.00		1.00	
average						
deprivation						
(<=0)						

1. Adjusted for age, socioeconomic status (education, marital status, social class, employment status)

2. Adjusted for age, socioeconomic status, lifetime GAD

3. Adjusted for age, socioeconomic status, lifetime GAD, physical diseases and disability

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

* Other: divorced, separated, widowed

* Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual
 * Prevalent physical disease: respiratory disease (asthma, bronchitis), allergies (allergies, hay fever), stroke,

heart attack, cancer, diabetes, thyroid conditions, arthritis

[¶] Below the median PCS value of 50.6

*The brackets show the reference categories that were used for each categorical variable when it was entered in the models - below average deprivation [ref] vs. above average deprivation; education: high [ref] vs. low; marital status: married [ref], single, others; social class: non-manual [ref] vs. manual; employment: yes [ref] vs. no; lifetime GAD: no [ref] vs. yes; prevalent physical disease: no [ref] vs. yes; disability level: low [ref] vs. high. These reference categories were based on the literature. Choosing other groupings for the potential confounders would not have changed the results. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

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Discussion

This research is an analysis based on EPIC-Norfolk data, and findings showed that living in an area of above average deprivation was associated with a significantly increased the risk of depression in men; the relationship with depression was not statistically significant in women. The association in men endured after adjusting for important individual-level confounders, such as serious physical health conditions, disability, and history of generalized anxiety disorder (GAD). When we looked closer to determine the specific component of area deprivation that has the greatest influence on men's mental health, unemployment emerged as an important factor. Men living in areas characterized by high unemployment had a 77% greater chance of having depression than those living in areas with low levels of unemployment.

Potential mechanisms

An environment in which deprivation is above average according to the Townsend index appears to differentially affect men and women's mental health after accounting for a number of potential confounders. A number of reasons can explain this. First, men appear to be more sensitive to stressful events occurring in their environment compared to women, especially if the stress is relating to financial and work-related problems.[25] The reason for this is that occupational and financial success is particularly important for men's mental health. Second, when living in disadvantaged regions, the possibility of hearing about job loss from others increases and this can promote anticipatory stress in those who are still working, which can increase their risk of depression.[48] This is particularly problematic for men who are perceived by their families as the main provider and head of household. In contrast, women's risk of depression seems to be influenced more by the social networks they are embedded in, the quality and continuity of relationships, the social support derived from neighbours and communities, and marital satisfaction.[25, 26] Women are more likely to experience depression as a result of unmet needs in relationships. Deficiencies in interpersonal relationships in women can lead to a perception that the self is unable to meet needs for self-worth and achievements, and this can increase their risk of poor mental health.[25] Men, on the other hand, have been shown to be more prone to depression as a

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result of failure at key instrumental tasks, including achievements at work and inability to provide for the family.[25, 49]

Unemployment, often accompanied by low social ranking, can lead to loss of self-esteem and role identity in men. This was seen in the United Kingdom after the 1970's, when the economy shifted from a manufacturing to a service-based one.[27] The shift was accompanied by a loss of skilled and semi-skilled jobs among men, while women had to enter the workforce and partake in jobs that were primarily service-based. The loss of employment opportunities among men might have contributed to a loss of role identity and self-esteem in this group.[27] However, even more than a decade later after this shift in economy, men who lost their employment and were in low social class groups showed poorer self-rated health compared to women. [50] This is also mirrored by recent research. [25] This again supports the notion that men are affected by failure at key instrumental tasks.[25] The same phenomenon occurred in rural areas of Midwestern United States after the farm crisis and related events occurred in the 1980s.[51] Rural areas held agrarian values, characterized by male provider norms and 'rugged independence'.[51] After the farm crisis hit, men were no longer able to fulfil their economic provider role, and both genders had to take on multiple jobs to make ends meet. This shook the traditional system, and created stress and contributed to high rates of depression in men. During this time, men also showed susceptibility to a wider range of stressors compared to women.[51]

Men and women also tend to experience and manifest the effect of stress in different ways. Women living in deprived areas have been shown to be more prone to anxiety[28], while men living in disadvantage are more likely to have depression. This could be a result of evolutionary, survival functions. Women have traditionally had the responsibility of childcare and ensuring the successful survival of future generations.[52] Therefore, living in circumstances of (above average) deprivation can trigger the fight or flight reaction, which can increase stress in finding ways to make ends meet so that they can raise their children. In this context, anxiety might be seen as protective, ensuring the survival of future generations. This is why women also tend to be more concerned about community features that can disrupt their caregiving role and negatively impact their family, such as, lack of safe play areas for children.[52, 53] Men have traditionally had the responsibility of being the

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provider, and if they are not able to fulfil this role, they are more likely to become depressed and potentially commit suicide.[25, 27] This is a problem in India, where suicide rates are high among male farmers whose crops have failed.[54, 55] In the UK, men with depression are also more likely than women to commit suicide. Taken together, these findings suggest that women may actually be more resilient than men when encountering adversity. However, very little research has examined this, and previous studies in the mental health literature have typically described women as vulnerable. Further research on health from a gendered perspective is needed.[28]

When exposed to the stresses and strains of deprivation, men are also more likely to develop substance abuse and this, in turn, can increase the risk for depression. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study[56] showed that total number of stressors experienced in life had a significantly stronger association with heavy drinking in men than in women. Experiencing stressors can also lead to unhealthy means of coping with the hardships, such as smoking and physical inactivity, and this can lead to sequelae.[24, 57] Finally, when men experience mental health issues, they are less likely to seek help than women [51].

Strengths and weaknesses and future research

This study shows that there is a statistically significant association between area deprivation and depression in men, while this relationship is not apparent in women. There are a number of strengths associated with our research. Our study used a structured questionnaire, the HLEQ, to assess mental health, and a measure of MDD was created using valid and reliable criteria stipulated by the DSM. Also, we were able to adjust for a number of important confounders, such as medical and psychiatric history, and sociodemographic factors, including unemployment measured at the level of the individual. Nonetheless, residual confounding may be present in our research if certain covariates were not adequately adjusted for. With respect to the medical history covariate, it is possible that some participants may have omitted disclosing or had difficulty recalling medical diagnoses and this might have introduced measurement error. Our measure of area deprivation also may not capture features of the environment that may affect mental health; however, all indexes designed to measure environmental effects suffer from this limitation. The Townsend index

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is theoretically sound and commonly used in research assessing these types of relationships. One of the limitations of this variable is that it is somewhat biased towards urban populations, particularly as it is capturing aspects that are more reflective of urban settings (ex. car ownership). Given that it may not be capturing rural deprivation as well as it should, measurement error may be an issue. This is an area of further research.

Because of healthy volunteer bias, it is possible that some of the sickest, most deprived people who would have been eligible to take part in EPIC-Norfolk, did not participate. This means that our results may not generalize to those individuals.

Also, we did not have information on length of living in the area for participants, however, migration in EPIC-Norfolk is minimal and unlikely to have biased the findings. People who took part in this study tended to reside in the same areas their whole lives. This is why Norfolk and the surrounding towns and rural areas were selected for participant recruitment.[58]

Another issue is the fact that EPIC-Norfolk only included people over the age of 40. As critical time periods for the development of depression include young adulthood[59], it would be useful if future research examined these relationships with deprivation using a younger sample. Nonetheless, depression can still develop at midlife and beyond, and many times, this is triggered by stressful life events, such as adverse social conditions.

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Subjective deprivation as a study limitation

A mechanism linking socioeconomic circumstances with depression in general involves subjective relative deprivation. Living in a deprived area can trigger comparison of the self to others, and this can in turn, lead to stress and poor mental health. A number of people living in deprived areas may experience negative emotions because they lack the necessary means to survive or are unable to achieve desired outcomes compared to those who are more affluent. Perceptions of lack can thus lead to poor health outcomes. Relative deprivation is composed of "affective and cognitive (i.e., appraisal) responses to perceived unfair outcomes."[60] Thus, social comparisons and stress arising from deprivation can contribute to increased risk of depression. A recent study has indeed shown that subjective relative deprivation is linked to depressive symptoms.[60] Living in a deprived area can give rise to subjective feelings of deprivation, which can subsequently lead to poor mental health. Although we did not have information on subjective feelings of deprivation, future studies should assess this.

Future research

Future research should assess the risk of depression not only in countries, such as, the US or UK where there is higher gender equality, but also in parts of the world where social roles and gendered norms for men and women have shown much less change over time. Countries with higher gender equality also show some of the highest rates of depression and other mental disorders in the world.[61] In Europe, the discrepancy in depression rates between men and women in highly-developed countries is greater than in less-developed countries where there is also greater gender inequality.[62] In Eastern European countries, levels of depression are similar between men and women[62], while in Western Europe, women are twice as affected as men.[63] More studies are needed to explore the influence of area deprivation on the mental health of men and women separately, and to do this in different contexts (ex. rural, urban) and countries around the world. Further, the reasons behind gender differences need to be better elucidated.

Finally, future studies should assess area deprivation and mental health at multiple points in time using a repeated measures analysis, because both may change over the follow-up period.

Placing our research in context

Although other studies have shown that the places in which people live have a substantial impact on health[14, 15], studies on the links between area deprivation and mental disorders from a gendered perspective are limited. A recent study[64] of over 1000 African American and non-Hispanic white adults living in the US showed that men who had experienced stressful life events in 1983-1986 were more likely to have depression in 2011, while this was not observed in women. This study, however, has limited generalizability, because it excluded other ethnicities. Also, the reliability and validity of the measure of stressful life events' that had occurred in the previous 3 years. Finally, exposure to stressful life events at the individual-level were investigated, rather than the effect of the place people live in.

A number of studies have assessed individual-level risk factors of depression, but substantially fewer have examined the influence of the environment on mental health. Nonetheless, studies of individual-level risk factors provide an important starting point in understanding relationships. Another prospective UK study of over 500 people[27] showed that the socioeconomic status of men at midlife was associated with depression at midlife, while this was not observed in women. For women, their socioeconomic status at birth influenced their levels of depression at midlife. Also, men who had experienced downward social mobility or a reduction in their socioeconomic status from adulthood to midlife were at high risk of having poor mental health at midlife, but this was not found in women.[27] These results suggest that women are more sensitive to the social class group they are in very early in life, while for men, social mobility over the life course, as well as the socioeconomic status group they are in during later life are more important for their mental health. This study, however, was limited, because it was based on a small sample size, assessed only individual-level measures rather than area-level level effects, and failed to adjust for a number of important confounders, such as, demographic factors. Failure to properly adjust for potential confounders can lead to overestimation of the effect estimate. Finally, this study examined general mental health, rather than individual psychiatric disorders.

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A recent US study showed that the types of stressors that influence men's risk of depression are those related to work, finances, and legal matters.[25] In this study, stressors were not

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linked to depression risk in women. Again, this research only assessed individual-level data. Our study shows, for the first time that living in an area of above average deprivation increases the risk of depression in men, while less so in women. Area deprivation was measured in our study at midlife and beyond, the time period which seems to have the greatest influence on men's mental health.[25]

Interpretation

The genders seem to be differentially affected by the environment, and we believe it is important to highlight this for policy-makers, clinicians, and public health authorities. Knowing that men living in areas of above average deprivation are more susceptible to depression can be used to tailor treatment and prevention efforts – and knowing how to best tailor treatment efforts and targeted interventions is important at a time when there are scarce health resources, such as now.

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

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

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

Data sharing: No additional data available.

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Appendix 1

Further information on A- and O-levels:

A-levels are advanced level qualifications, which "are subject-based qualifications that can lead to university, further study, training, or work." (UCAS)

According to IGCSE Centre, "O-Level is the abbreviation of Ordinary Level. It is one of the two-part GCE (General Certificate of Education). The other part of GCE is Advanced Level (A-Level), which students enter after completing O-Level. O-Level is the final certification for secondary school, to be taken at fifth form or year 11 at approximately age 17 (or age group 14-16). Students that have completed O-Level are considered to have complemented formal education." (IGCSE Centre)

Distribu		
	tion of Townsend index sc	ores
1.	Above average deprivatior	ı
<u>Men</u>		
Mean: 1	.96	
Standar	d deviation: 1.49	
Range:	0.01 to 6.09	
<u>Women</u>		
Mean: 1	93	
Standar	d deviation: 1.47	
Range:	0.01 to 6.98	
2.	Below average deprivation	ı Z.
<u>Men</u>		
Mean: -	2.85	
Standar	d deviation: 1.21	
Range:	-6.73 to -0.02	
Women	L	
Mean: -	2.83	
Standar	d deviation: 1.21	
Range:	-6.10 to -0.02	

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Appendix 3

Odds ratios for MDD according to individual- and area-level characteristics for men and women who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

	Men (n	=8,236)	Women (n=10,335)			
	Odds ratios	and 95% Cl ¹	Odds ratios	and 95% Cl ¹		
Characteristic*						
Individual-level variables		-	·	•		
Socio-						
demographics Age						
(per 10 years) E ducation [‡]	0.47 (0.38, 0.59)	<0.0001	0.59 (0.51, 0.69)	<0.0001		
Low	1.00 (0.69, 1.45)	0.9977	1.30 (1.01, 1.67)	0.0384		
High	1.00		1.00			
Marital status						
Single	1.41 (0.72, 2.79)	0.3181	0.91 (0.47, 1.75)	0.7737		
Married	1.00		1.00			
Other [*]	3.58 (2.42, 5.28)	<0.0001	2.36 (1.85, 3.02)	<0.0001		
Social class [¥]						
Manual	1.06 (0.76, 1.49)	0.7340	0.97 (0.76, 1.24)	0.8204		
Non-manual	1.00		1.00			
Employment [¥]						
No	2.24 (1.49, 3.37)	0.0001	1.55 (1.18, 2.04)	0.0019		
Yes	1.00		1.00			
Health status						
Lifetime GAD						
Yes	12.65 (8.71, 18.37)	<0.0001	7.37 (5.57, 9.75)	<0.0001		
No	1.00		1.00			
Prevalent physical						
disease						
Yes⁺	1.25 (0.90, 1.73)	0.1842	1.25 (0.99, 1.59)	0.0658		
No	1.00		1.00			
Disability level						
High [¶]	1.98 (1.38, 2.83)	0.0002	1.41 (1.11, 1.80)	0.0048		
Low	1.00		1.00			
Area-level variable						
Townsend index						
Deprivation Above average	1.51 (1.03, 2.21)	0.0358	1.24 (0.94, 1.64)	0.1325		

1			
2			
3	deprivation		
4	(>0)		
5	Below	1.00	1.00
6		1.00	1.00
7	average		
8	deprivation		
9	(<=0)		
10			
11			us, lifetime GAD, physical diseases and disability
12			ree; low education: refers to no education
13		l, separated, widowed	
14			non-skilled; non-manual: professionals, managerial, skilled non-manual
15			y disease (asthma, bronchitis), allergies (allergies, hay fever), stroke,
16		er, diabetes, thyroid	conditions, arthritis
17		an PCS value of 50.6	
18			gories that were used for each categorical variable when it was entered
19 20			ation [ref] vs. above average deprivation; education: high [ref] vs. low;
20			ners; social class: non-manual [ref] vs. manual; employment: yes [ref] vs.
21			alent physical disease: no [ref] vs. yes; disability level: low [ref] vs. high.
22			sed on the literature. Choosing other groupings for the potential
23 24	confounders wou	ld not have changed t	he results.
24 25			he results.
26			
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		nbers (column on the right) and the explanations provided. t of items that should be included in reports of observational studies	Enseignement by copyright, including for uses related to	Jopen-2018-027530 on 25
	Item No	Recommendation	or uses i	Line numbers within the article
Fitle 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 	6, jateer to to	er 2019. Dc
ntroduction		O _k	to text and 89	an l
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	894	
Dbjectives Methods	3	State specific objectives, including any prespecified hypotheses	150	<u> </u>
Study design	4	Present key elements of study design early in the paper	1 mining 11g	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	 158≱17 tra	
Participants	6	 (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—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 Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case 	nidggand similar technologies.	We specify in the paper that the Townsend wiss record linked to the cohort. on June 14, 2025 at Age
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	187-29	n@ Bib
Data sources/ neasurement	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		We re two variables of interest in this study: area

Page 45 d	of 49		BMJ Open	ıjopen-2018-02 1 by copyright
1 2 3 4 5 6			more than one group	arce potential confounders – in the methods I list them all and the set of th
7	Bias	9	Describe any efforts to address potential sources of bias	
8	Study size	10	Explain how the study size was arrived at	325 m 5 180 B 5
9 10	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,	How analyses: 306-313
11			describe which groupings were chosen and why	(the gap hods section describes how the variables were
12 13				categories were used)
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16				reference categories of the variables in the footnotes
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18 10				of E ariables was done in accordance with the
19 20				literature and provide the relevant citations in the
21				methods section.
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23 24				Hor the dependent variable was created: 187-220
25				How are a-level measure was created: 269-286
26				Indevideal-level measures: 222-267
27	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	29 = 35 6
28 29			(b) Describe any methods used to examine subgroups and interactions	Singilargo other studies, I conducted analyses
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32				significance), but rather, because I felt it was
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35				rationa for conducting sex-specific analyses.
36				Knowin which gender group is more affected can
37				help with the tailoring of targeted interventions.
38 39			(c) Explain how missing data were addressed	We ind dated that this was a complete-case analysis.
40			(d) Cohort study—If applicable, explain how loss to follow-up was addressed	Loss to follow-up was not a problem in this study.
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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	udia 188 for Novem En
		(b) Give reasons for non-participation at each stage	We do not have the reasons for non-participation, be the set of the study way is the set of the study way is the set of the study way is the set of the study way is the set of
		(c) Consider use of a flow diagram	Were the end of the en
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	We provided characteristics for those with vs. without MDD, because we felt it was important to show the characteristics of those exposed vs. non-exposed (see alse Tagle 1)
		(b) Indicate number of participants with missing data for each variable of interest	292-295 we had to move this section to the Method because one of the reviewers had asked us to do so.
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Inigally we mentioned that participants were followed for 7 years, however, we had to delete this phose because one of the reviewers had asked us to do to the Townsend index was record linked to the coort.
Outcome data	15*	Cohort study-Report numbers of outcome events or summary measures over time	38 6 ,38 8 ,
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	at Ager
		Cross-sectional study-Report numbers of outcome events or summary measures	
Main results	16	(<i>a</i>) 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 and 3 contain unadjusted and progressively adjusted estimates. We also discussed the findings within the text, and provide odds ratios and 95%
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			in Eg	Foults section to reduce redundancy. However,
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			<u> </u>	to do so.
		(b) Report category boundaries when continuous variables were categorized		Secut-offs are provided. In regards to the
				and index, the methods section states that those
			below ?	and above the cut-point of zero were compared.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful	ABES)	fron
		time period		
Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity analyses		ty analyses: 1) relationship between area
				agon and pure MDD (past-year GAD
				(a); 2) correlated data analysis replaced with
			· · ·	eregression ; 3) analyses run with education re-
			0-	rized and ethnicity included ; 4) Townsend
				devided into quintiles.
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Discussion			gie s.	
Key results	18	Summarise key results with reference to study objectives	470-47	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	556-59	b
		Discuss both direction and magnitude of any potential bias	2	enc:
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	655-66	(We also have a section comparing our study
		analyses, results from similar studies, and other relevant evidence	results	those of others: 616-652, as well as a section
			on pote	extial mechanisms explaining our findings: 481-
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3 - 4	Generalisability 21	Discuss the generalisability (external validity) of the study results
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10 11	*Give information sepa	rately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in the provide the provided and the
13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42	checklist is best used in	nd Elaboration article discusses each checklist item and gives methodological background and published groups of transparent reporting. The STROBE conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.groups of transparent reporting. The STROBE Initiative is available at www.groups-statement.org.
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The association between area deprivation and major depressive disorder in British men and women: a cohort study

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23	14	Olivia Remes ¹ , Louise Lafortune ¹ , Nick Wainwright ² , Paul Surtees ¹ , Kay-Tee Khaw ³ , Carol
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3	31	ABSTRACT
4	32	
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6 7	34	OBJECTIVE
8	34 35	Studies have shown area-level deprivation can increase the risk for mental disorders over and
9		above individual-level circumstances, such as education and social class. The objective of this
10	36	· · · · · · ·
11	37	study is to determine whether area deprivation is associated with major depressive disorder
12	38	(MDD) in British women and men separately while adjusting for individual-level factors.
13 14	39	
14	40	DESIGN
16	41	Large, population study.
17	42 43	SETTING
18	43 44	UK population-based cohort.
19		ok population-based conort.
20	45	
21 22	46	PARTICIPANTS
23	47	30,445 people from the general population aged 40 years and older and living in England
24	48	consented to participate at study baseline, and of these, over 20,000 participants completed
25	49	a structured Health and Life Experiences Questionnaire (HLEQ) used to capture MDD. Area
26	50	deprivation was measured in 1991 using Census data, and current MDD was assessed in 1996-
27 28	51	2000. 8,236 men and 10,335 women had complete data on all covariates.
20	52	
30	53	PRIMARY OUTCOME MEASURE
31	54	MDD identified according to the Diagnostic and Statistical Manual of Mental Disorders, fourth
32	55	edition (DSM-IV).
33	56	
34 35	57	RESULTS
36	58	In this study, 3.3% (339/10,335) of women and 2.1% (177/8,236) of men had MDD. Men living
37	59	in the most deprived areas were 51% more likely to have depression than those living in areas
38	60	that were not deprived (OR=1.51, 95% CI: 1.01 to 2.24; p=0.043), but the association between
39	61	deprivation and MDD was not statistically significant in women (OR=1.24, 95%CI: 0.93 to 1.65;
40 41	62	p=0.143).
42	63	
43	64	CONCLUSION
44	65	This study shows that the residential environment differentially affects men and women, and
45	66	this needs to be taken into account by mental health policy-makers. Knowing that men living
46 47	67	in deprived conditions are at high risk for having depression helps inform targeted prevention
47 48	68	and intervention programs.
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We used a population-based sample of over 20,000 British adults and controlled for

We used a structured questionnaire (the Health and Life Experiences Questionnaire of the EPIC-Norfolk study) to determine whether participants met criteria for MDD

We used the Townsend index to assess area deprivation. This index is commonly-used

People who took part in EPIC-Norfolk were generally more affluent and healthier than

those living in other parts of England. As such, our results may not be generalizable

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important confounders, including social class, medical history, and disability.

by researchers to examine deprivation and is a theoretically sound measure.

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5 6	72	Strengths and limitations of this study
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10	74	important confounders, includir
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14 15	78	according to the DSM.
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Introduction Depression is a common psychiatric disorder affecting approximately 350 million people around the world.[1] According to the Global Burden of Disease Study[2], major depressive disorder (MDD) contributed to 689.9 per 100,000 disability-adjusted life years in men and 1161.2 per 100,000 disability-adjusted life years in women in 2010. Depression can increase the risk for impairment, disability and suicide.[3, 4, 5] It has also been linked to decreased work productivity, poor quality of life, and high health service use.[3, 6, 7] A number of studies have examined the individual-level risk factors of depression, such as, personal and parental history of psychopathology[8], genetics[9], history of trauma and stressful life events[10, 11], and socioeconomic status.[12] However, the environment or living context can have a profound influence on mental health, over and above individual-level factors.[13, 14, 15] In a systematic review[16] of 14 studies, about half found an association between neighbourhood socioeconomic conditions and depression. Living in an area of low socioeconomic status can expose people to a higher number of stressors, such as, violence, disorder, and noise pollution, and this can have deleterious effects on mental health.[17] There is a wealth of literature on the effect of the places where people live on mental health. Findings from systematic reviews[18, 19, 20] assessing neighbourhood characteristics and depression show that there is large heterogeneity in findings, because of differences in study populations, the confounders that are adjusted for in analyses, and the measures and definitions used to delineate neighbourhoods.[19] Although there is much evidence on the influence of area-level disadvantage or deprivation on depression, research on this relationship from a gendered perspective is lacking. In this large, population-based, cohort study, we examine the association between area deprivation and major depressive disorder in men and women separately, while controlling

psychiatric co-morbidity, and disability. Area deprivation refers to residential environments
 or living contexts characterized by factors, such as, high levels of unemployment, non-home

for a range of important confounders, including social class, previous medical conditions,

Page 5 of 51

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ownership, non-car ownership, and low income.[13] Findings are disaggregated by gender, and this is done for several reasons. Gender frames access to resources derived from the environment.[21, 22] Compared to men, women have been shown to have less access to material and social conditions, such as income, power, and social status, and this can influence mental health. Women have historically been the victims of discrimination, and because of this have had limited opportunities for education, and well-remunerated and respected forms of employment.[23] Women have taken on different job roles and tasks than men, which has exposed them to different hazards and contaminants affecting their health. Women have traditionally been seen as 'care-takers' in society and involved in domestic work, which might have led to an interruption in their education or career paths. As such, they have derived fewer resources with which they could maintain or improve their health.[23, 24]

However, there are additional reasons why findings are disaggregated by gender. Women and men tend to react to different kinds of stressors. Recent research has shown that men are more susceptible to work- and finance-related stressors, while women are more affected by deficiencies in their social networks and interpersonal relationships. [25, 26] This research is based on a study conducted in the US and other parts of the world. Hence, living in a deprived area with high levels of unemployment might be particularly detrimental for men's mental health. This was evident when the economy shifted in the UK from a manufacturing-to a service-based one, and many men lost their jobs.[27] Prior to the shift, the local economy had relied on skilled and semi-skilled jobs, typically performed by men. When the economy changed, an increasing number of women entered employment (occupying mainly service industry jobs), and this had implications for traditional gender-defined social roles. Men who experienced reduced economic opportunities may have suffered from loss of role identify and self-esteem, and this had consequences for their physical and mental health.[27] A recent study[25] showed that men's mental health is particularly affected if they fail at key instrumental tasks, such as, work achievements and ability to provide for the family. In contrast, women are more likely to be depressed if they fail to meet their needs for relationship.[25] To this end, it appears that men and women are susceptible to different kinds of stressors.

150 It remains unclear whether men and women living in areas of above average deprivation are
151 differentially susceptible to MDD – the objective of this study will be to assess this. Knowing
152 that one gender is at risk of developing depression when exposed to deprived circumstances
153 helps to tailor interventions and allocate scarce resources according to need.[28] This is
154 particularly important at a time of scarce economic and health-related resources.

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1 2		
3 4 5 6 7 8 9 10	156	Methods
	157	
	158	Data were drawn from EPIC-Norfolk, whose design and study methods have been described
	159	in detail elsewhere.[29] In brief, a prospective population-based cohort of 30,445 participants
11	160	ages 40 to 74 years were recruited by post between 1993 and 1997 through general practice
12 13 14 15 16 17 18 19 20 21 22	161	age-sex registers in the city of Norwich and the surrounding small towns and rural areas. At
	162	baseline (1993-97), participants completed a postal Health and Life Experiences (HLQ)
	163	questionnaire that captured information on sociodemographics, including age, gender,
	164	highest educational attainment, marital status, social class, employment status, ethnicity and
	165	self-reported physician diagnoses of physical diseases. Using participants' postal codes, a
	166	measure of area deprivation was derived based on the 1991 Census. Between 1993 and 2000,
23 24	167	participants completed self-reported postal questionnaires provided they: 1) were still alive,
25 26 27 28 29 30 31 32 33	168	2) did not ask to be removed from the study's mailing list, and 3) had a valid mailing address.
	169	
	170	During 1996-2000, 20,919 participants completed a structured, psychosocial Health and Life
	171	Experiences (HLEQ) questionnaire. During this time, an assessment of generalized anxiety
	172	disorder (GAD) and major depressive disorder (MDD) was made according to the Diagnostic
34 35	173	and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[30]. Using the HLEQ
36 37	174	questionnaire, disability measures based on the SF-36 were also derived.[31]
38 39	175	
40 41	176	All participants recruited through general-practice registers and who completed a baseline
42 43	177	health questionnaire were eligible to be included in our study; those who completed a
44	178	psychosocial questionnaire during follow-up were eligible to be included in our analysis.
45 46	179	
47 48	180	In regards to the study size, an initial sample of 30,445 participants completed the baseline
49 50	181	HLQ and of these, 20,921 filled out the psychosocial HLEQ. After retaining the people with
51 52	182	complete measures on all covariates, the final sample size was 18,571.
53 54	183	
55	184	Although EPIC-Norfolk is a prospective study and area derivation was measured in 1991 and
56 57	185	anxiety in 1996-2000, this analysis should be considered cross-sectional.
58 59 60	186	

1 2		
3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24	187	Dependent variable
	188	The primary outcome in this study was current MDD, which was measured using the HLEQ, a
	189	structured self-assessment instrument designed to provide a measure of depression for
	190	inclusion in a large-scale epidemiology project.[32, 33] DSM-IV criteria were applied to the
	191	psychiatric symptoms to determine whether participants had an episode of MDD that was
	192	ongoing at the time of the completion of the HLEQ questionnaire. Participants who reported
	193	a psychiatric episode were asked to estimate the onset and offset timings of the episode, and
	194	then to report an outline of the history of the problem. Participants were also asked about
	195	age at first symptom onset and subsequent episode recurrence.
	196	
	197	The dependent variable in this study is current MDD, defined as an episode of MDD reported
	198	as ongoing at the time of the completion of the HLEQ.
25 26	199	
27 28	200	The following two core criteria of MDD were first evaluated:
29	201	
30 31 32 33 34 35	202	1. Have there ever been times in your life when you felt sad or depressed for two weeks or
	203	more in a row?
	204	2. Have there ever been times in your life when you lost interest in most things like your work
36 37	205	or activities that usually give you pleasure, for two weeks or more in a row?
38	206	
39 40	207	If participants answered yes to one of these questions, they were then asked to think of the
41 42	208	most recent two-week episode during their lives when these feelings of sadness, depression
43 44	209	or loss of interest were the worst. They then had to report that these feelings of being sad,
45 46	210	depressed, or loss of interest lasted all day or most of the day, and that during these two
47 48	211	weeks of their most recent episode, they felt this way every day or almost every day.
49	212	
50 51	213	In addition, at least five of the following symptoms had to be present: gaining or losing weight,
52 53 54 55 56 57 58 59	214	having trouble falling asleep or sleeping too much, feeling tired or low on energy, feeling
	215	unable to sit still or feeling slowed down, experiencing guilt or shame, feeling worthless, losing
	216	confidence, having trouble concentrating, and thinking a lot about death or suicide. One of
	217	these five symptoms had to be one of the two core criteria evaluated at the beginning.
60	218	

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 Finally, it was evaluated whether these symptoms interfered with participants' lives andresulted in disability or impairment.

8
 9 222 Individual-level measures (potential confounders)

Individual-level measures included age, education, employment status, marital status, social class, health status, ethnicity, history of anxiety, and prevalent physical disease. The final categorization of the variables took cell size into account and was also done in accordance with previous literature.[33-39] Age was divided into 10-year bands. Educational attainment was categorized into high (vocational or formal qualifications at the A- or O-level or degree-level qualifications) vs. low (no formal qualifications). Further details on the meaning of A-and O-level can be found elsewhere [40, 41]; the appendix also contains definitions of these (appendix 1). Employment was divided into yes vs. no. Marital status was categorized into three groups: married, single (or never married), and others (widowed, divorced, separated). Social class was derived using the Computer-Assisted Standard Occupational Coding[42] and categorized as follows: I (professionals), II (managerial and technical occupations), III non-manual and III manual (skilled workers), IV (partly skilled workers), and V (unskilled manual workers). To assign social class to men and women, the male partner's current or past occupation was used. If this information was not available, the female partner's occupation was used. If the social class from either partner was unavailable, then it was coded as missing. The final categorization of social class included manual: skilled manual, partly skilled, and unskilled; and non-manual: professionals, managerial and technical, and skilled non-manual. Individual-level health status was assessed through the construction of a variable capturing major prevalent physical diseases. This was based on HLQ questions asking participants: "Has the doctor ever told you that you have any of the following?", followed by a list of options, such as allergies, asthma, cancer, stroke, heart attack, diabetes, thyroid conditions, etc. Ethnicity was based on a self-reported question asking participants to tick the relevant box: 'white', 'black Caribbean', 'black other', 'Indian', 'Pakistani', 'Bangladeshi', 'Chinese', 'other'.

Lifetime history of GAD was also assessed using the self-reported HLEQ questionnaire.[33] Lifetime GAD consisted of having ever had at least one episode that met core criteria stipulated by the DSM-IV. Anxiety was identified if participants reported having uncontrollable, excessive worry for six months or longer on most days than not that resulted

Page 10 of 51

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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.

To determine disability levels, we used the physical component summary (PCS) derived from the HLEQ. The PCS is part of the SF-36, a widely-used, validated self-assessment tool. The SF-36 is a 36-item measure capturing 8 health dimensions: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy/vitality, bodily pain, and general health perception. The eight dimensions of the SF-36 were used to create two higher order scores, one of which was the PCS. Higher scores indicate better health.[31] PCS scores were dichotomized above and below the median.

All of these individual-level variables were regarded as potential confounders and selected based on the literature and their association with depression and area-level socioeconomic circumstances.

35 268

³⁶ 269 Area-level measure (exposure variable) ³⁷

To examine area deprivation, we used the Townsend Index. [43, 44] This is one of the most commonly-used measures of area deprivation in the UK and particularly appropriate for the time of the original EPIC-Norfolk study. This index is a composite measure of four variables obtained from the 1991 Census: 1) percentage of economically active residents over age 16 who are unemployed, 2) percentage of households that do not possess a car, 3) percentage of private households that are not owner occupied, and 4) percentage of private households that are overcrowded (have more than 1 person per room). These variables were obtained at the level of the enumeration district, which is a geographic area used for census purposes in Britain. Each variable was standardized by obtaining Z scores (dividing the mean by the standard deviation across enumeration districts in England). The Z values of the four variables were added together to produce a Townsend index score for each enumeration district. A score of 0 represents the national mean, while positive values of the index indicate enumeration districts that are above average deprivation, while negative values indicate

Page 11 of 51

BMJ Open

those that are below average deprivation. The postal codes of participants were record linked
to enumeration districts, and participants were considered to live in areas of above average
deprivation depending on the Townsend index score assigned to their enumeration
district.[43]

288 Depending on the results from the main analysis (association between overall area 289 deprivation and depression), the Townsend deprivation index was disaggregated into its four 290 constituent components to determine whether any one of these is associated with MDD.

3 291

292 Missing data

The number of missing observations for each covariate were: 9 for education, 47 for marital status, 417 for MDD, 434 for GAD, 458 for social class, 75 for the Townsend index, and 1386 for the SF-36, 52 for employment status.

27 296

297 Statistical analysis

First, we compared participants on sociodemographic, and medical and psychiatric history characteristics, and the prevalence of MDD was computed for sub-groups. Next, we undertook correlated data analysis based on generalized estimating equations (GEE)[45, 46] to determine the population-average effect of living in an area of above average deprivation on risk of having depression while controlling for confounders. MDD is a dichotomous outcome and the intra-cluster correlation was assumed to be equal. As such, we used GEE with a logit link and an exchangeable correlation structure. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

First, we ran unadjusted analyses between deprivation and MDD. To determine the influence of potential confounders on risk of having depression, we progressively adjusted the models and accounted for 1) age, educational attainment, marital status, and social class; then for 2) age, educational attainment, marital status, social class, and GAD; and finally for 3) age, educational attainment, marital status, social class, GAD, physical diseases and disability level. We conducted separate analyses for men and women. The individual-level covariates were sociodemographics, and medical and psychiatric history, while the area-level covariate was the Townsend index score. The progressively adjusted models allowed us to estimate adjusted odds ratios (OR) and 95% confidence intervals based on robust standard errors.

A dichotomous variable was created using the Townsend index scores, and 0 was used as the cut-point (considered to be the national average). The variable was dichotomized, because we wanted to compare participants' scores to the national average[47] - scores above the cut-point of 0 were considered above average deprivation. A binary variable was also used in accordance with previous research[47] and because of cell size considerations – we wanted to ensure that there were sufficient people with MDD in each category of the deprivation variable.

Models were constructed for participants with complete measurements on all covariates. It was not possible to group the MDD variable otherwise since it was created and categorized according to the DSM-IV[32, 33], and area deprivation was analysed in accordance with the literature[37, 43].

Several sensitivity analyses were undertaken. We ran fully-adjusted models using pure MDD as the outcome, in which those with past-year GAD were excluded. It should be mentioned that although GAD and MDD have been regarded as closely correlated by many researchers, they are independent disorders. The high GAD-MDD comorbidity found in older literature was due to the use of clinical populations with multiple co-occurring conditions.

Next, we disaggregated the index used to measure disadvantage. If a significant relationship was found between area deprivation and depression for one of the genders in a fully-adjusted model, we investigated further. We disaggregated the Townsend index into its 4 constituent components (unemployment, non-home ownership, non-car ownership, and overcrowding) to determine whether any aspect of deprivation is associated with increased risk of having depression in that gender group. Each component was dichotomized using a cut-point of 0, because it represents the national average.

Then we determined whether relationships held after dividing the Townsend index into quintiles and adjusting for sociodemographic and health status variables. Further, we examined whether the inclusion of additional covariates or recategorization of variables made any difference to the effect estimates. We included ethnicity as a potential confounder

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3 4 5 6 7 8 9	346	in a fully-adjusted model, and assessed whether the division of the education variable into
	347	four categories influenced the associations.
	348	
	349	Finally, we conducted logistic regression, which does not take the intra-cluster correlation
10 11	350	into account, and compared the findings to those from GEE. Similar results between the
12 13	351	models suggests that the intraclass correlation is negligible.
14 15 16 17	352	
16	353	All models used two-sided statistical tests, and a p-value of <0.05 was considered statistically
18	354	significant. Statistical Analysis Software (SAS) Version 9.3 (SAS Institute, Cary, NC) was used
19 20	355	in these analyses.
21 22	356	
23 24	357	Patient and Public Involvement:
25 26 27 28 29 30 31 32 33	358	
	359	There were no patients or public involved in the development of the research question,
	360	outcome measures, design of the study, or recruitment to and conduct of the study.
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1 2		
3 4	363	Results
5 6	364	
7 8	365	At baseline, 30,445 participants were recruited from general practices in the city of Norwich
9	366	and the surrounding towns and rural areas. Of these, 20,919 people completed the HLEQ
10 11	367	during the follow-up period. In total, 18,571 out of 20,919 (89%) people were available for
12 13	368	analysis, because they had complete data on all covariates.
14 15	369	
16 17	370	In this sample, there were 8,236 men and 10,335 women over the age of 40 years. Table 1
$\begin{array}{c} 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 54\\ 55\\ 56\\ 57\\ 58\\ 59\\ 60\\ \end{array}$	371	shows the distribution of individual- and area-level characteristics by current MDD.

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372 Table 1: Distribution of characteristics for women and men who completed the HLEQ

373 questionnaire in the EPIC-Norfolk cohort

Women (n=10,335)		Men (n=8,236)			
Characteristic	Number with characteristic	Percentage and number with MDD	Number with characteristic	Percentage and number with MDD	
Individual-level					
variables					
Socio-demographics					
Age (years)	0				
<50	1450	5.0 (72) ^{<i>a</i>}	964	3.4 (33) ^{<i>a</i>}	
50-60	3716	3.9 (145)	2651	3.0 (80)	
60-70	3180	2.1 (68)	2743	1.5 (40)	
>70	1989	2.7 (54)	1878	1.3 (24)	
Education [‡]					
Low	4050	3.5 (141)	2365	2.2 (51)	
High	6285	3.2 (198)	5871	2.1 (126)	
Marital status					
Single	417	2.4 (10) ^a	303	3.6 (11) ^a	
Married	7750	2.7 (207)	7237	1.7 (122)	
Other [*]	2168	5.6 (122)	696	6.3 (44)	
Social class [¥]					
Manual	3829	3.3 (127)	3286	2.3 (76)	
Non-manual	6506	3.3 (212)	4950	2.0 (101)	
Employment					
Yes	4075	128 (3.1)	3821	68 (1.8) ^b	
No	6260	(3.4) 211	4415	109 (2.5)	
Health status					
Prevalent physical			4		
disease					
Yes ⁺	5698	3.8 (214) ^b	3843	2.6 (100) ^b	
No	4637	2.7 (125)	4393	1.8 (77)	
Disability level					
High¶	5296	3.9 (208) ^a	4021	3.0 (119) ^a	
Low	5039	2.6 (131)	4215	1.4 (58)	
Lifetime GAD					
Yes	448	19.4 (87) ^a	255	22.4 (57) ^a	
No	9887	2.5 (252)	7981	1.5 (120)	
Area-level variable					
Townsend index					

1 2						
2 3 4		Above average	1646	4.6 (76) ^a	1242	3.6 (45) ^a
5 6		deprivation (>0) Below average	8689	3.0 (263)	6994	1.9 (132)
7 8	~	deprivation (<=0)				
9	374 375			ion of the Townsend index ee; low education: refers to		vomen.
10 11	376 377	* Other: divorced, sepa		disease (asthma and brond	chitis) allergies (alle	rgies and hay fever)
12 13	378	stroke, heart attack, car	ncer, diabetes, th	yroid conditions, arthritis		
14 15	379 380	[¶] Below the median PC		on-skilled; non-manual: pr	ofessionals, manage	rial, skilled non-manual
16	381 382	^a P < 0.001 ^b P < 0.05				
17 18						
19 20						
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Page 17 of 51

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The prevalence of (current) MDD was 2.1% (177/8236) for men and 3.3% (339/10335) for women. Women with MDD were younger than 50 years of age, more likely to be divorced/separated/widowed, have prevalent physical disease, high disability, GAD, and live in areas of above average deprivation. Among men, similar patterns emerged (table 1). Men with MDD were also more likely to be unemployed.

After performing correlated data analysis based on GEE, findings showed that the risk of depression in men living in areas of above average deprivation was 95% higher in an unadjusted analysis (OR=1.95, 95% Cl: 1.39, 2.76; p=0.0001) (results not shown). After accounting for sociodemoraphics, the odds ratio attenuated slightly to 1.57 (OR=1.57, 95% Cl: 1.09, 2.26; p=0.0152) (table 2).

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Table 2: Odds ratios for MDD according to individual- and area-level characteristics for

395 men (n=8,236) who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

			Odds ratios a	nd 95% Cl		
Characteristic*	Model A ¹	P-value for model A	Model B ²	P-value for model B	Model C ³	P-value for Model C
Individual-level variables						
Socio-						
demographics						
Age						
(per 10 years)	0.40 (0.32,	<0.0001	0.50 (0.40,	< 0.0001	0.47 (0.38,	<0.0001
	0.50)		0.63)		0.60)	
Education [‡]						
Low	1.10 (0.76,	0.6081	1.06 (0.72,	0.7813	1.00 (0.68,	0.9978
	1.61)		1.54)		1.46)	
High	1.00		1.00		1.00	
Marital status						
Single	1.46 (0.76,	<0.0001	1.39 (0.71,	<0.0001	1.41 (0.72,	<0.0001
	2.83)		2.68)		2.76)	
Married	1.00		1.00		1.00	
Other [*]	3.66 (2.53,		3.48 (2.31,		3.58 (2.39,	
	5.28)		5.22)		5.35)	
Social class [¥]						
Manual	1.02 (0.73,	0.9161	1.14 (0.81,	0.4612	1.06 (0.76,	0.7298
	1.41)		1.59)		1.48)	
Non-manual	1.00		1.00		1.00	
Employment [¥]						
No	3.69 (2.48,	<0.0001	2.64 (1.74,	<0.0001	2.24 (1.46,	0.0002
	5.50)		4.03)		3.45)	
Yes			1.00		1.00	
Health status						
Lifetime GAD						
Yes			14.33 (9.84,	<0.0001	12.65 (8.68,	<0.0001
			20.87)		18.44)	
No			1.00		1.00	
Prevalent						
physical						
disease						
Yes⁺					1.25 (0.89 <i>,</i>	0.1977

1								
2								
3 4		No					1.00	
5		Disability level						
6		High¶					1.98 (1.39,	0.0002
7							2.82)	
8 9		Low					1.00	
10		Area-level						
11		variable						
12		Townsend						
13 14		index						
15		Deprivation						<u> </u>
16		Above	1.57 (1.09,	0.0152	1.56 (1.05,	0.0287	1.51 (1.01,	0.0434
17		average	2.26)		2.31)		2.24)	
18 19		deprivation			,			
20		(>0)						
21		Below	1.00		1.00		1.00	
22		average						
23 24		deprivation						
25		(<=0)						
26	397	((=0)						
27	398	1. Adjusted for age	, sociodemograp	hics (educatio	n, marital status, s	ocial class, e	mployment statu	s)
28 29	399	2. Adjusted for age	, sociodemograp	hics, lifetime (GAD			
30	400	3. Adjusted for age					-	х
31	401 402	 Prevalent physica heart attack, cance 	•), allergies (a	illergies, hay teve	r), stroke,
32	403	[¥] Manual: skilled m				fessionals, m	nanagerial, skilled	non-manual
33 34	404	[‡] High education:	O-level, A-level, d	legree; low ea	lucation: refers to		-	
35	405		separated, wido					
36	406 407	[¶] Above the media	in PCS value of 50).6				
37	407	*The brackets show	v the reference c	ategories that	were used for eac	h categorica	l variable when it	was entered
38 39	409	in the models - dep		-		-		
40	410	[ref] vs. low; marita						
41	411 412	employment: yes [i disability level: low						. yes;
42	412	uisability level. low	[lei] vs. liigh. li		categories were t			
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The OR reduced slightly after controlling for lifetime GAD (OR=1.56, 95% CI: 1.05, 2.31; p=0.029), but remained highly significant. After additionally adjusting for prevalent physical diseases and disability, the effect estimate became somewhat attenuated (OR=1.51, 95% CI: 1.01, 2.24; p=0.043), however, a statistically significant association between area derivation and depression remained (table 2). As the association with area deprivation emerged to be statistically significant for men (table 2), we took this finding further and wanted to determine the specific component of deprivation that was related to men's risk of having poor mental health (by disaggregating the Townsend index into its constituent components). Results showed that the OR was highest for unemployment (OR=1.77, 95% CI: 1.16, 2.71; p=0.008), followed by non-car ownership (OR=1.20, 95% CI: 0.70, 2.04; p=0.507), and lowest for overcrowding (OR=0.93, 95% CI: 0.60, 1.42; p=0.727) and non-home ownership (OR=0.81, 95% CI: 0.49, 1.34; p=0.422). Of these, only the effect estimate for unemployment was statistically significant (Appendix 3). Men living in areas characterized by high levels of unemployment were almost 80% more likely to have depression than those living in areas with low levels of unemployment. Next, we wanted to determine whether deprivation is associated with pure MDD, and thus excluded past-year GAD; the association with depression remained statistically significant (OR=1.64, 95% CI: 1.06, 2.52; p=0.025).

In women, while there was a statistically significant association in the unadjusted analysis (OR=1.55, 95% 1.19, 2.01; p=0.0010) as well as in the model adjusting for sociodemographics (OR=1.40, 95% CI: 1.07, 1.84; p=0.013), the association lost its significance in the fully-adjusted model (OR=1.24, 95%CI: 0.93, 1.65; p=0.143) (table 3). Thus, we did not carry out further analyses using the Townsend index.

We also conducted some sensitivity analyses. First, we divided the Townsend index into quintiles. Results showed that men living in the most deprived quintile had a statistically significantly increased risk for depression (OR=1.68, 95% CI: 1.01, 2.79; 0.0472), while none of the quintiles for women showed statistically significant findings. Second, we wanted to determine whether there was any change in findings after incorporating ethnicity in the original fully-adjusted models. The associations remained the same (men: OR=1.53, 95% CI: 1.03, 2.27 and women: OR=1.25, 95% CI: 0.94, 1.66). Second, we undertook analyses in which the education variable was left in its original form (divided into 4 categories: no education, O- Page 21 of 51

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level, A-level, degree and beyond) in fully-adjusted models, and similar findings were again obtained (men: OR=1.51, 95% CI: 1.02, 2.24) and women: OR= OR=1.23, 95% CI: 0.92, 1.63). Third, we re-ran the fully-adjusted models using logistic regression rather than correlated data analysis based on GEE (Appendix 4), and results remained essentially unchanged (men: OR=1.51, 95% CI: 1.03, 2.21 and women: OR=1.24, 95% CI: 0.94, 1.64). This shows that there indeed is a robust association between overall area deprivation and depression in men, while there is no statistically significant effect in women. for perteries only

Table 3: Odds ratios for MDD according to individual- and area-level characteristics for

455	women (n=10,335) who completed the HLEQ questionnaire in the EPIC-Norfolk cohort
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			Odds ratios an	d 95% Cl		
Characteristic*	Model A ¹	P-value for model A	Model B ²	P-value for model B	Model C ³	P-value for Model C
Individual-level variables						
Socio- demographics Age	~					
(per 10 years)	0.54 (0.46, 0.64)	<0.0001	0.62 (0.52, 0.74)	<0.0001	0.59 (0.50 <i>,</i> 0.71)	<0.0001
Education [‡]					- /	
Low	1.23 (0.97 <i>,</i> 1.56)	0.0890	1.29 (1.01, 1.65)	0.0412	1.30 (1.02, 1.66)	0.0356
High	1.00		1.00		1.00	
Marital status						
Single	0.93 (0.48, 1.78)	<0.0001	0.91 (0.48, 1.75)	<0.0001	0.91 (0.47, 1.75)	<0.0001
Married	1.00		1.00		1.00	
Other [*]	2.56 (2.00, 3.27)		2.41 (1.87, 3.10)		2.36 (1.83, 3.04)	
Social class [¥]						
Manual	0.95 (0.75, 1.21)	0.6964	0.99 (0.77, 1.27)	0.9530	0.97 (0.76, 1.25)	0.8225
Non-manual Employment [¥]	1.00		1.00		1.00	
No	1.87 (1.42 <i>,</i> 2.48)	<0.0001	1.62 (1.21, 2.15)	0.0010	1.55 (1.17, 2.06)	0.0026
Yes			1.00		1.00	
Health status						
Lifetime GAD						
Yes			7.97 (5.99 <i>,</i> 10.60)	<0.0001	7.37 (5.52, 9.83)	<0.0001
No			1.00		1.00	
Prevalent						
physical						
disease						
Yes⁺					1.25 (0.98, 1.59)	0.0682
No					1.00	

1								
2								
3		Disability level						
4		-					1 11 /1 11	0.0045
5		High¶					1.41 (1.11,	0.0045
6							1.79)	
7		Low					1.00	
8		Area-level						
9 10		variable						
11		Townsend						
12		index						
13								
14		Deprivation						
15		Above	1.40 (1.07,	0.0132	1.26 (0.95, 1.67)	0.1081	1.24 (0.93,	0.1425
16		average	1.84)				1.65)	
17		deprivation						
18		(>0)						
19 20		Below	1.00		1.00		1.00	
20			1.00		1.00		1.00	
22		average						
23		deprivation						
24		(<=0)						
25	456							
26	457	1. Adjusted for ag	e, sociodemograph	nics (educati	on, marital status, soo	cial class, e	mployment statu	s)
27	458		e, sociodemograpł					
28	459				GAD, physical disease			
29 30	460				education: refers to no	o educatio	า	
30	461		l, separated, widow					
32	462				d; non-manual: profe		-	
33	463				(asthma, bronchitis),	allergies (a	illergies, hay feve	r), stroke,
34	464 465		er, diabetes, thyro an PCS value of 50		s, arthritis			
35	465 466	" Below the mean	an PCS value of 50	.0				
36	400	*The brackets sho	w the reference c	ategories th	at were used for each	categoric	al variable when i	t was entered
37	468			-] vs. above average d	-		
38	469				al class: non-manual [
39	470				sical disease: no [ref]			
40	471		ategories were bas			U,		
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Discussion This research is an analysis based on EPIC-Norfolk data, and findings showed that living in an area of above average deprivation was associated with a significantly increased the risk of depression in men; the relationship with depression was not statistically significant in women. The association in men endured after adjusting for important individual-level confounders, such as serious physical health conditions, disability, and history of generalized anxiety disorder (GAD). When we looked closer to determine the specific component of area deprivation that has the greatest influence on men's mental health, unemployment emerged as an important factor. Men living in areas characterized by high unemployment had a 77% greater chance of having depression than those living in areas with low levels of unemployment. **Potential mechanisms** An environment in which deprivation is above average according to the Townsend index appears to differentially affect men and women's mental health after accounting for a number of potential confounders. A number of reasons can explain this. First, men appear to be more sensitive to stressful events occurring in their environment compared to women, especially if the stress is relating to financial and work-related problems.[25] The reason for this is that occupational and financial success is particularly important for men's mental health. Second, when living in disadvantaged regions, the possibility of hearing about job loss from others increases and this can promote anticipatory stress in those who are still working, which can increase their risk of depression.[48] This is particularly problematic for men who are perceived by their families as the main provider and head of household. In contrast, women's risk of depression seems to be influenced more by the social networks they are embedded in, the quality and continuity of relationships, the social support derived from neighbours and communities, and marital satisfaction.[25, 26] Women are more likely to experience depression as a result of unmet needs in relationships. Deficiencies in interpersonal relationships in women can lead to a perception that the self is unable to meet needs for self-worth and achievements, and this can increase their risk of poor mental health.[25] Men, on the other hand, have been shown to be more prone to depression as a For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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result of failure at key instrumental tasks, including achievements at work and inability toprovide for the family.[25, 49]

Unemployment, often accompanied by low social ranking, can lead to loss of self-esteem and role identity in men. This was seen in the United Kingdom after the 1970's, when the economy shifted from a manufacturing to a service-based one.[27] The shift was accompanied by a loss of skilled and semi-skilled jobs among men, while women had to enter the workforce and partake in jobs that were primarily service-based. The loss of employment opportunities among men might have contributed to a loss of role identity and self-esteem in this group.[27] However, even more than a decade later after this shift in economy, men who lost their employment and were in low social class groups showed poorer self-rated health compared to women. [50] This is also mirrored by recent research. [25] This again supports the notion that men are affected by failure at key instrumental tasks.[25] The same phenomenon occurred in rural areas of Midwestern United States after the farm crisis and related events occurred in the 1980s.[51] Rural areas held agrarian values, characterized by male provider norms and 'rugged independence'.[51] After the farm crisis hit, men were no longer able to fulfil their economic provider role, and both genders had to take on multiple jobs to make ends meet. This shook the traditional system, and created stress and contributed to high rates of depression in men. During this time, men also showed susceptibility to a wider range of stressors compared to women.[51]

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Men and women also tend to experience and manifest the effect of stress in different ways. Women living in deprived areas have been shown to be more prone to anxiety[28], while men living in disadvantage are more likely to have depression. This could be a result of evolutionary, survival functions. Women have traditionally had the responsibility of childcare and ensuring the successful survival of future generations.[52] Therefore, living in circumstances of (above average) deprivation can trigger the fight or flight reaction, which can increase stress in finding ways to make ends meet so that they can raise their children. In this context, anxiety might be seen as protective, ensuring the survival of future generations. This is why women also tend to be more concerned about community features that can disrupt their caregiving role and negatively impact their family, such as, lack of safe play areas for children.[52, 53] Men have traditionally had the responsibility of being the

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provider, and if they are not able to fulfil this role, they are more likely to become depressed and potentially commit suicide. [25, 27] This is a problem in India, where suicide rates are high among male farmers whose crops have failed. [54, 55] In the UK, men with depression are also more likely than women to commit suicide. Taken together, these findings suggest that women may actually be more resilient than men when encountering adversity. However, very little research has examined this, and previous studies in the mental health literature have typically described women as vulnerable. Further research on health from a gendered perspective is needed.[28]

When exposed to the stresses and strains of deprivation, men are also more likely to develop substance abuse and this, in turn, can increase the risk for depression. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study[56] showed that the total number of stressors experienced in life had a significantly stronger association with heavy drinking in men than in women. Experiencing stressors can also lead to unhealthy means of coping with the hardships, such as smoking and physical inactivity, and this can lead to sequelae.[24, 57] Finally, when men experience mental health issues, they are less likely to seek help than women [51].

35 552

553 Strengths and weaknesses and future research

This study shows that there is a statistically significant association between overall area deprivation and depression in men, while this relationship is not apparent in women. There are a number of strengths associated with our research. Our study used a structured questionnaire, the HLEQ, to assess mental health, and a measure of MDD was created using valid and reliable criteria stipulated by the DSM. Also, we were able to adjust for a number of important confounders, such as medical and psychiatric history, and sociodemographic factors, including unemployment measured at the level of the individual. Nonetheless, residual confounding may be present in our research if certain covariates were not adequately adjusted for. With respect to the medical history covariate, it is possible that some participants may have omitted disclosing or had difficulty recalling medical diagnoses and this might have introduced measurement error. Our measure of area deprivation also may not capture features of the environment that may affect mental health; however, all indexes designed to measure environmental effects suffer from this limitation. The Townsend index

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is theoretically sound and commonly used in research assessing these types of relationships.
One of the limitations of this variable is that it is somewhat biased towards urban populations,
particularly as it is capturing aspects that are more reflective of urban settings (ex. car
ownership). Given that it may not be capturing rural deprivation as well as it should,
measurement error may be an issue. This is an area of further research.

573 Because of healthy volunteer bias, it is possible that some of the sickest, most deprived people 574 who would have been eligible to take part in EPIC-Norfolk, did not participate. This means 575 that our results may not generalize to those individuals.

Also, we did not have information on length of living in the area for participants, however,
migration in EPIC-Norfolk is minimal and unlikely to have biased the findings. People who
took part in this study tended to reside in the same areas their whole lives. This is why Norfolk
and the surrounding towns and rural areas were selected for participant recruitment.[58]

Another issue is the fact that EPIC-Norfolk only included people over the age of 40. As critical time periods for the development of depression include young adulthood[59], it would be useful if future research examined these relationships with deprivation using a younger sample. Nonetheless, depression can still develop at midlife and beyond, and many times, this is triggered by stressful life events, such as adverse social conditions. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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Subjective deprivation as a study limitation A mechanism linking socioeconomic circumstances with depression in general involves subjective relative deprivation. Living in a deprived area can trigger comparison of the self to others, and this can in turn, lead to stress and poor mental health. A number of people living in deprived areas may experience negative emotions because they lack the necessary means to survive or are unable to achieve desired outcomes compared to those who are more affluent. Perceptions of lack can thus lead to poor health outcomes. Relative deprivation is composed of "affective and cognitive (i.e., appraisal) responses to perceived unfair outcomes."[60] Thus, social comparisons and stress arising from deprivation can contribute to increased risk of depression. A recent study has indeed shown that subjective relative deprivation is linked to depressive symptoms.[60] Living in a deprived area can give rise to subjective feelings of deprivation, which can subsequently lead to poor mental health. Although we did not have information on subjective feelings of deprivation, future studies should assess this.

603 Future research

Future research should assess the risk of depression not only in countries, such as, the US or UK where there is higher gender equality, but also in parts of the world where social roles and gendered norms for men and women have shown much less change over time. Countries with higher gender equality also show some of the highest rates of depression and other mental disorders in the world.[61] In Europe, the discrepancy in depression rates between men and women in highly-developed countries is greater than in less-developed countries where there is also greater gender inequality.[62] In Eastern European countries, levels of depression are similar between men and women[62], while in Western Europe, women are twice as affected as men.[63] More studies are needed to explore the influence of area deprivation on the mental health of men and women separately, and to do this in different contexts (ex. rural, urban) and countries around the world. Further, the reasons behind gender differences need to be better elucidated.

55 616

Finally, future studies should assess area deprivation and mental health at multiple points in
 time using a repeated measures analysis, because both may change over the follow-up
 period.

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3 4	620	Placing our research in context
5 6	621	Although other studies have shown that the places in which people live have a substantial
7 8	622	impact on health[14, 15], studies on the links between area deprivation and mental disorders
9	623	from a gendered perspective are limited. A recent study[64] of over 1000 African American
10 11	624	and non-Hispanic white adults living in the US showed that men who had experienced
12 13	625	stressful life events in 1983-1986 were more likely to have depression in 2011, while this was
14 15	626	not observed in women. This study, however, has limited generalizability, because it excluded
16	627	other ethnicities. Also, the reliability and validity of the measure of stressful life events was
17 18	628	not reported – the measure was based on a checklist of 'major negative events' that had
19 20	629	occurred in the previous 3 years. Finally, exposure to stressful life events at the individual-
21 22	630	level were investigated, rather than the effect of the place people live in.
23 24	631	
25	632	A number of studies have assessed individual-level risk factors of depression, but substantially
26 27	633	fewer have examined the influence of the environment on mental health. Nonetheless,
28 29	634	studies of individual-level risk factors provide an important starting point in understanding
30 31	635	relationships. Another prospective UK study of over 500 people[27] showed that the
32	636	socioeconomic status of men at midlife was associated with depression at midlife, while this
33 34	637	was not observed in women. For women, their socioeconomic status at birth influenced their
35 36	638	levels of depression at midlife. Also, men who had experienced downward social mobility or
37 38	639	a reduction in their socioeconomic status from adulthood to midlife were at high risk of having
39		
40 41	640	poor mental health at midlife, but this was not found in women.[27] These results suggest
42 43	641	that women are more sensitive to the social class group they are in very early in life, while for
44 45	642	men, social mobility over the life course, as well as the socioeconomic status group they are
46	643	in during later life are more important for their mental health. This study, however, was
47 48	644	limited, because it was based on a small sample size, assessed only individual-level measures
49 50	645	rather than area-level level effects, and failed to adjust for a number of important
51 52	646	confounders, such as, demographic factors. Failure to properly adjust for potential
53	647	confounders can lead to overestimation of the effect estimate. Finally, this study examined
54 55	648	general mental health, rather than individual psychiatric disorders.
56 57	649	
58 59	650	A recent US study showed that the types of stressors that influence men's risk of depression

A recent US study showed that the types of stressors that influence men's risk of depression are those related to work, finances, and legal matters.[25] In this study, stressors were not

linked to depression risk in women. Again, this research only assessed individual-level data. Our study shows, for the first time that living in an area of above average deprivation increases the risk of depression in men, while less so in women. Area deprivation was measured in our study at midlife and beyond, the time period which seems to have the greatest influence on men's mental health.[25]

Interpretation

The genders seem to be differentially affected by the environment, and we believe it is important to highlight this for policy-makers, clinicians, and public health authorities. Knowing that men living in areas of above average deprivation are more susceptible to depression can be used to tailor treatment and prevention efforts – and knowing how to best tailor treatment efforts and targeted interventions is important at a time when there are scarce health resources, such as now.

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46 47	689	Data sharing: The data for this study are available in the supplementary materials. Further
48 49	690	questions could be sent to OR (or260@medschl.cam.ac.uk).
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Appendix 1

Further information on A- and O-levels:

A-levels are advanced level qualifications, which "are subject-based qualifications that can lead to university, further study, training, or work." (UCAS)

According to IGCSE Centre, "O-Level is the abbreviation of Ordinary Level. It is one of the two-part GCE (General Certificate of Education). The other part of GCE is Advanced Level (A-Level), which students enter after completing O-Level. O-Level is the final certification for secondary school, to be taken at fifth form or year 11 at approximately age 17 (or age group 14-16). Students that have completed O-Level are considered to have completed formal education." (IGCSE Centre)

Distrib	ution of Townsend index scores	Appendix 2
DISTID	ution of Townsena maex scores	
1.	Above average deprivation	
<u>Men</u>		
Mean:	1.96	
Standa	ard deviation: 1.49	
Range:	: 0.01 to 6.09	
<u>Wome</u>	<u>n</u>	
Mean:	1.93	
Standa	ard deviation: 1.47	
Range:	: 0.01 to 6.98	
2.	Below average deprivation	
<u>Men</u>		
Mean:	-2.85	
Standa	ard deviation: 1.21	
Range:	: -6.73 to -0.02	
<u>Wome</u>	<u>n</u>	
Mean:	-2.83	
Standa	ard deviation: 1.21	

Appendix 3

Odds ratios for MDD according to individual- and area-level characteristics for men who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

Odds ratios and 95% Cl			
Characteristic*	Model C ¹	P-value for Model C	
Individual-level variables	·		
Socio-demographics	<u>^</u>		
Age			
(per 10 years)	0.47 (0.38, 0.59)	<0.0001	
Education [‡]	(,		
Low	1.01 (0.69, 1.48)	0.9420	
High	1.00	0.9120	
Marital status	1.00		
Single	1.39 (0.71, 2.69)	<0.0001	
Married	1.00	<0.0001	
Other [*]			
Social class [¥]	3.51 (2.32, 5.29)		
		0 7747	
Manual	1.05 (0.75, 1.47)	0.7747	
Non-manual	1.00		
Employment [¥]	\sim		
No	2.23 (1.45, 3.42)	0.0002	
Yes	1.00		
Health status			
Lifetime GAD			
Yes	12.65 (8.68, 18.43)	<0.0001	
No	1.00		
Prevalent physical			
disease			
Yes⁺	1.24 (0.88, 1.74)	0.2176	
No	1.00		
Disability level			
High [¶]	2.01 (1.41, 2.86)	0.0001	
Low	1.00	0.0001	
Area-level variable	1.00		
Townsend index			
Deprivation			
Unemployment		0.0004	
Yes (>0)	1.77 (1.16, 2.71)	0.0084	
No (<=0)	1.00		
Non-car ownership			
Yes (>0)	1.20 (0.70, 2.04)	0.5067	
No (<=0)	1.00		
Non-home ownership			
Yes (>0)	0.81 (0.49, 1.34)	0.4220	
No (<=0)	1.00		

Overcrowding

Yes (>0)	0.93 (0.60, 1.42)) 0.7272
No (<=0)	1.00	
	cociedomegraphics lifetim	

1. Adjusted for age, sociodemographics, lifetime GAD, physical diseases and disability

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

* Other: divorced, separated, widowed

[¥] Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual

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

[¶] Below the median PCS value of 50.6

*The brackets show the reference categories that were used for each categorical variable when it was entered in the models - below average deprivation [ref] vs. above average deprivation; education: high [ref] vs. low; marital status: married [ref], single, others; social class: non-manual [ref] vs. manual; employment: yes [ref] vs. no; lifetime GAD: no [ref] vs. yes; prevalent physical disease: no [ref] vs. yes; disability level: low [ref] vs. high These reference categories were based on the literature.

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Appendix 4

Odds ratios for MDD according to individual- and area-level characteristics for men and women who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

	Men (n	=8,236)	Women (n=10,335)		
	Odds ratios and 95% Cl ¹		Odds ratios and 95% Cl ¹		
Characteristic*					
ndividual-level variables					
Socio-					
demographics Age					
per 10 years) Education [‡]	0.47 (0.38, 0.59)	<0.0001	0.59 (0.51, 0.69)	<0.0001	
Low	1.00 (0.69, 1.45)	0.9977	1.30 (1.01, 1.67)	0.0384	
High	1.00		1.00		
Marital status					
Single	1.41 (0.72, 2.79)	0.3181	0.91 (0.47, 1.75)	0.7737	
Married	1.00		1.00		
Other [*]	3.58 (2.42, 5.28)	<0.0001	2.36 (1.85, 3.02)	<0.0001	
Social class [¥]					
Manual	1.06 (0.76 <i>,</i> 1.49)	0.7340	0.97 (0.76, 1.24)	0.8204	
Non-manual	1.00		1.00		
Employment [¥]					
No	2.24 (1.49, 3.37)	0.0001	1.55 (1.18, 2.04)	0.0019	
Yes	1.00		1.00		
lealth status					
ifetime GAD					
Yes	12.65 (8.71, 18.37)	<0.0001	7.37 (5.57, 9.75)	<0.0001	
No	1.00		1.00		
Prevalent					
physical					
disease					
Yes*	1.25 (0.90, 1.73)	0.1842	1.25 (0.99, 1.59)	0.0658	
No	1.00		1.00		
Disability level					
High [¶]	1.98 (1.38, 2.83)	0.0002	1.41 (1.11, 1.80)	0.0048	
Low	1.00		1.00		
Area-level /ariable					
Fownsend ndex					
Deprivation					
Above average	1.51 (1.03, 2.21)	0.0358	1.24 (0.94, 1.64)	0.1325	

deprivation			
(>0)			
Below	1.00	1.00	
average			
deprivation			
(<=0)			
1. Adjusted for a	ge, sociodemographics, l	ifetime GAD, physical diseases and disability	
		e; low education: refers to no education	
	ed, separated, widowed		
		on-skilled; non-manual: professionals, managerial, ski	
	icer, diabetes, thyroid co	disease (asthma, bronchitis), allergies (allergies, hay f	ever), stroke,
	dian PCS value of 50.6		
		pries that were used for each categorical variable who	en it was entered
		on [ref] vs. above average deprivation; education: h	
		rs; social class: non-manual [ref] vs. manual; employr	
		ent physical disease: no [ref] vs. yes; disability level:	low [ref] vs. high.
These reference	categories were based o	n the literature.	

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	Item No	Recommendation	Ens	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 	6, 4 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	er
Introduction		0r	to text and a	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	89	
Objectives	3	State specific objectives, including any prespecified hypotheses	150	5 <u>4</u>
Study design	4	Present key elements of study design early in the paper	a minitag	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		7 273
Participants	6	 (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—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 Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case 	(0	79. We specify in the paper that the Townsend wins record linked to the cohort. on June 14, 2025 at Age
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	187-29	n 969 Bib
Data sources/ neasurement	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		where two variables of interest in this study: area

Page 47 of 51			BMJ Open	ıjopen-2018-02 d by copyright,
1 2 3 4 5 6			more than one group	are potential confounders – in the methods I list them all and bate how they were assessed and mention that the way were collected through the baseline, self-reported postal ILQ questionnaire.
7	Bias	9	Describe any efforts to address potential sources of bias	
8	Study size	10	Explain how the study size was arrived at	<u>32</u> 18 使 路安
9 10 11 12 13 14	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: 306-313 (the Hathods section describes how the variables were categories ded/which categories were used)
15 16 17 18 19 20				When the property of the variables in the footnotes under the variables in the footnotes under the variables in the footnotes under the variables in the variables in the variables in the variables in the under the variables was done in accordance with the literature and provide the relevant citations in the
21 22 23 24 25 26			erien	methods section. How the dependent variable was created: 187-220 How area-level measure was created: 269-286 Indevideal-level measures: 222-267
27 28	Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	29 5 35 6
20 29 30 31 32 33 34 35 36 37 38			(<i>b</i>) Describe any methods used to examine subgroups and interactions	Singilar to other studies, I conducted analyses separated y for men and women. I did not do this beguse of p-value considerations (statistical significance), but rather, because I felt it was important to do. In the introduction, I provide the rational for conducting sex-specific analyses. Knowing which gender group is more affected can help with the tailoring of targeted interventions.
39			(c) Explain how missing data were addressed	We ind ated that this was a complete-case analysis.
40 41 42 43 44 45 46			(<i>d</i>) Cohort study—If applicable, explain how loss to follow-up was addressed For peer review only - http://bmjopen.bmj.com/site/about/guidelines.	Loss to follow-up was not a problem in this study.

BMJ Open	s Were were able to track down all participants using
Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	vartous means, unless they expressed that they wished f to be repoved from the mailing list. We elaborate on this in the manuscript.
(e) Describe any sensitivity analyses	4, 2025 at ogies.
For peer review only - http://bmjopen.bmj.com/site/about/guideline	Agence Bibliographique de l

ge 49 of 51		BMJ Open	jopen-20
Results			jopen-2018-027530 ol l by copyright, includ
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	udi 18ຜູ້18ຜູ້ for use
		(b) Give reasons for non-participation at each stage	We do not have the reasons for non-participation, be we we have a data were not collected when the study way way in the study way is a study way in the study way is a study way in the study way is a
		(c) Consider use of a flow diagram	Were the end of the en
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	We provided characteristics for those with vs. without MDD, because we felt it was important to show the characteristics of those exposed vs. non-exposed (see alsa.Tagle 1)
		(b) Indicate number of participants with missing data for each variable of interest	292-292- we had to move this section to the Method because one of the reviewers had asked us to do so.
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	Inistally we mentioned that participants were followed for 7 years, however, we had to delete this phase because one of the reviewers had asked us to do bo. The Townsend index was record linked to the coort.
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	38.5. 25
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	at Ager
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(<i>a</i>) 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	adjuster estimates. We also discussed the findings within the text, and provide odds ratios and 95%
		4 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.	xhtml d

		BMJ Open	open-ż by cop	Pa be intervals.
			018-u yrigh	د
			comfided	e intervals.
			udincia:	dded the confounders based on the literature –
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				As per strobe, we included this information
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			t 0 0	sults section to reduce redundancy. However,
			- <u>0</u> .~	tor would like us to repeat this information in
			ື້ດເບລີ	s, we are happy to do so.
		(b) Report category boundaries when continuous variables were categorized	9 A T	cut-offs are provided. In regards to the
				d index, the methods section states that those
		No	below and	ad above the cut-point of zero were compared.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful	from t (ABES) ta mini	i ا
		time period		
Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity analyses		ty analyses: 1) relationship between area
				on and pure MDD (past-year GAD
			m); 2) correlated data analysis replaced with
				egression; 3) analyses run with education re-
				ed and ethnicity included ; 4) Townsend
				vided into quintiles.
			In Hither	se instances, the associations remained the
			sange. Jun	
			hn	
			Thē is to	eported in the paper.
Discussion			2025 gies.	
Key results		Summarise key results with reference to study objectives	474-48 ¥	-
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.	560-60 4	<u>i</u>
		Discuss both direction and magnitude of any potential bias		
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of	ם בי	(We also have a section comparing our study
		analyses, results from similar studies, and other relevant evidence	(Ō	those of others: 620-656, as well as a section
			phi	tial mechanisms explaining our findings: 485-
		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.x	.xhtml de	,)
			D	-

Page 51 of	51		BMJ Open	,	d by cop	jopen-2
1 2				55	vright, In	2018-0275
3 ⁻ 4 -	Generalisability	21	Discuss the generalisability (external validity) of the study results	57	hckiding	76
	Other information	n			ding	n 2
6	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for	674	द् 67	72
7 8 9			the original study on which the present article is based	674	Ensei uses ro	vembe
10 11			rately for cases and controls in case-control studies and, if applicable, for exposed and unexposed g	Í	äΞ	19
14	checklist is best u	sed in	Ind Elaboration article discusses each checklist item and gives methodological background and pub conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.pla and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available		uperieur (ABES) . xtrand data mining, Al training, and similar technologies.	 Description
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