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A longitudinal study of blood folate levels and depressive symptoms among young women in the Southampton Women's Survey

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Abstract

Objective—Lower blood folate levels have been associated with depression in cross-sectional surveys, but no studies have examined the relationship prospectively to determine whether the relationship is causal. We designed a follow-up study to examine whether lower blood folate predicts incident depressive symptoms.

Design—Women aged 20 to 34 years registered in general practices in Southampton, UK were asked to participate. Baseline assessment included the general health questionnaire (GHQ-12) measure of anxiety and depression, and socioeconomic factors, diet, smoking, and alcohol intake. Two years later participants' general practice (GP) records were examined for evidence of incident symptoms of depression.

Results—At baseline 5051 women completed the GHQ-12 and had red cell folate levels measured, of whom 1588 (31.4%) scored above the threshold for case level symptoms of anxiety and depression on the GHQ-12. Two years later GP records for 3996 (79.1%) were examined, but 1264 with baseline evidence of depression were excluded from follow-up analysis. Incident depressive symptoms were recorded for 307 (11.2%) of the remaining 2732. Lower red cell folate levels were associated with caseness on the GHQ-12 (adjusted prevalence ratio 0.99 per 100nmol/l red cell folate, 95% CI 0.98 to 1.00). No relationship was found between red cell folate levels and incident depressive symptoms over two years (adjusted hazard ratio 0.99 (95%CI: 0.96 to 1.02).

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AUTHOR CONTRIBUTIONS

Hazel Inskip, Keith Godfrey and Cyrus Cooper designed and managed the Southampton Women's Survey. Sian Robinson provided expert advice on the nutritional aspects of the study. Tony Kendrick originated the idea for the depression work within the cohort, supported by Nick Dunn. Anne Oestmann helped design the data collection instruments and led on the collection of the GP record data. Hazel Inskip conducted the analyses, and Tony Kendrick wrote the first draft of the paper. Hazel Inskip had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the interpretation of the findings and to the writing of the paper. All approved the final version of the manuscript.

DECLARATION OF INTERESTS

All the authors declare that they have no competing interests in relation to this paper.

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Conclusions—Low folate levels were not associated with subsequent depressive symptoms. This suggests that lower red cell folate levels may be a consequence rather than a cause of depressive symptoms.

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BACKGROUND

Epidemiological and biological evidence suggests low folate may be a risk factor for depression[1;2]. A recent systematic review of three case-control studies[3-5], seven cross-sectional community surveys[6-12], and one cohort study[13] demonstrated that lower folate levels are associated with depression and this relationship holds after adjustment for possible confounders including socio-economic status and lifestyle factors including body mass index, smoking and alcohol consumption[14].

The association could be bidirectional as on the one hand folate deficiency may result from poor appetite and reduced dietary intake in depression and on the other folate deficiency may lead to depression. Several mechanisms could link low folate status to depression, including effects on neurotransmitter synthesis, reduction in methylation reactions leading to lower S-adenosyl methionine and raised homocysteine levels, and direct effects on the central nervous system[2;15-17]. There is some evidence that folic acid may be an effective treatment for depression or adjunct to antidepressants[18] which also suggests low folate could be a causal factor, or could be involved in the maintenance of depression once established. The important question is whether folic acid supplementation might prevent depression at a population level[14].

To date no studies have examined the relationship between blood folate status and depression in a prospective study. There has been one prospective study of dietary folate intake and subsequent risk of depression. Tolmunen *et al* recruited 2682 middle-aged Finnish men and found that lower energy-adjusted dietary intake of folate was associated with a higher risk of a hospital discharge diagnosis of depression over 11 to 16 years of follow-up[13]. Their results suggest interventions to increase folate intake may help prevent depression.

However, dietary intake of folate is only an indirect measure of intracellular folate status, which can be assessed directly through estimation of red blood cell folate level. Furthermore, both depression and nutritional status are less of a problem for middle-aged men than for women of child bearing age, or the elderly, and so studies are needed in these groups. The recent systematic review called for more longitudinal studies to explore the direction of causality between low folate and depression[14]. We present data on red cell folate levels and the subsequent risk of incident depressive symptoms over two years in a large cohort of young women in the Southampton Women's Survey.

METHODS

Study population

The Southampton Women's Survey (SWS) was established in 1998 to study women of child-bearing age and follow them through subsequent pregnancies. The aim was to assess

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the influence of maternal factors operating before and during pregnancy on the growth and development of the foetus and child. Between 1998 and 2002 all general practitioners (GPs) in Southampton were asked to help recruit their female patients aged 20–34 years.

Recruitment

A small team of SWS staff acted under contract to the GPs to recruit eligible women; excluding any the GPs felt should not be approached. A letter and leaflet explaining the study were sent to each woman, followed by a telephone call. If the woman was willing, a research nurse visited her at home. Further measures were used to recruit women who could not be contacted by phone and those not registered with GPs. Fully informed written consent was obtained before baseline assessment.

Of those women contacted about the study, 12 579 (around 75%) agreed and were interviewed by a research nurse. All interviews were conducted between April 1998 and October 2002. They provided information on diet, body composition, socio-economic circumstances, physical activity, and lifestyle including exercise, smoking, and alcohol consumption. Full details of the survey have been published[19]. Following initial interview, those women who were willing provided a venous blood sample in the luteal phase of their menstrual cycle. From this, red cell folate was measured using microparticle enzyme immunoassay. Part way through initial recruitment a depression component was added to the study, and was approved by the Southampton and South West Hampshire NHS Research Ethics Committee in November 1999 (reference 335/99).

Baseline measure of anxiety and depression

From March 2000, all SWS women were asked at initial interview to complete the 12-item version of the General Health Questionnaire (GHQ-12) to measure baseline symptoms of depression[20]. The GHQ-12 is a short screening instrument with good sensitivity for depression but is not specific, and also picks up anxiety and other mental health problems[20]. Participating women also gave written consent for subsequent examination of their general practice (GP) medical records for evidence of incident depression in the two years following interview.

For each of the GHQ-12 questions, there are four response options. The two items indicating a lower likelihood of depression were each scored as 0 and the other two as 1 (0-0-1-1 scoring method)[20]. The scores were summed across the 12 questions and those with a score of ≥3 were categorised as having ‘case level’ symptoms of anxiety or depression at baseline.

Follow-up measure of depressive symptoms

Two or more years after initial interview, the GP records were examined for evidence of incident symptoms of depression in the two years following interview. Data were collected by one of two researchers (AO and JB) who recorded depressive symptoms; treatment with antidepressants; referrals to counselling, psychology, or psychiatric services for depression; and/or hospital episodes of depression. The written text describing the symptoms was checked by a GP member of the research team (TK) to ensure it represented depression rather than alternative mental health problems; anxiety symptoms in the absence of

depression were not included. Both researchers and the research GP were blind to participants' folate status.

Statistical analysis

Initial analysis focused on whether the women were classified as having case level symptoms of anxiety or depression according to the GHQ-12 at baseline. Poisson regression with robust variance[21] was used to estimate prevalence ratios for case level symptoms in relation to folate levels.

Cox regression was performed to examine the risk of a new episode of depressive symptoms in the two-year period following initial interview. This analysis was restricted to women who were not classified as having case level anxiety or depression according to the GHQ-12 at baseline and were not identified in the GP notes as already being treated for depression at the start of the follow-up period.

Red cell folate levels were considered as a continuous variable for the main analysis of association with depressive symptoms. Folate levels were also categorised, firstly by dividing them into five equal strata, and secondly by dividing the lowest 10% from the remaining 90%.

The second categorisation was used to assess any evidence of a threshold effect at particularly low folate levels. Tests for trend (P_{trend}) were based on the continuous measure of red cell folate. Hazard ratios were also calculated after adjustment for potentially confounding socio-economic factors (age, educational attainment, social class, receipt of social security benefits, and perceived financial strain[22]) and lifestyle variables (smoking, alcohol consumption, strenuous exercise, and body mass index (BMI)).

RESULTS

From March 2nd 2000, 7210 women participated in the SWS of whom 7020 (97.4%) completed the GHQ-12 questionnaire. Red cell folate levels were available for 5051 women (71.9%), of whom 1588 (31%) scored above the threshold for case level symptoms of anxiety and depression on the GHQ-12 at baseline.

After two years the records of 3996 women (79.1%) were available to be examined for incident symptoms of depression, of whom 1264 had evidence of existing depression at baseline and were excluded from follow-up analysis (1224 scored ≥3 on the GHQ-12 and a further 40 had existing depression recorded in GP records). Incident depressive symptoms over the two year follow-up period were recorded for 307 (11.2%) of the remaining 2732. Of these, 269 (87.6%) received at least one intervention (244 were treated with antidepressants, 15 received other treatment in the practice, 52 were referred for counselling, 30 referred to Psychiatry, and 2 admitted to hospital).

Table 1 shows baseline characteristics of participating women. The distribution of all factors considered at baseline is comparable to the main SWS dataset. Previously, the SWS has been shown to be broadly representative of England and Wales as a whole[19]. Table 1 shows that those who were followed-up and for whom we had folate levels were broadly

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representative of all those assessed for symptoms of anxiety and depression at baseline, although levels of unemployment, perceived stress, and perceived financial strain were slightly lower among those followed up.

Those who gave blood for folate were very similar to the whole group in terms of their GHQ-12 scores. Those who didn't give blood were slightly more likely to have case level symptoms (34% compared with 31% among those who did), but median scores for the two groups were identical.

Table 2 and Figure 1 show the results of the cross-sectional analysis relating red cell folate, in five equal strata, to the prevalence of case level symptoms of anxiety and depression on the GHQ-12. A strong relationship with folate was found in an unadjusted analysis with a prevalence ratio for 'caseness' of 0.98 per 100nmol/l red cell folate (95% confidence interval (CI) 0.97 to 0.99, p = 0.005). Adjustment for socio-economic and lifestyle variables that were also significantly associated with baseline caseness and folate levels (perceived financial strain, exercise, and BMI), weakened the relationship considerably (prevalence ratio 0.99, 95% CI 0.98 to 1.00, p = 0.05).

Table 3 and Figure 2 show results of the analysis relating red cell folate to the risk of incident symptoms of depression among those not identified as being depressed at baseline, categorising folate in five equal strata.

There was no clear suggestion of a relationship with depression in the predicted direction and, using the continuous measure of folate, the unadjusted hazard ratio per 100nmol/l was 0.99 (95%CI: 0.96 to 1.02, p = 0.4); after adjustment for socioeconomic and lifestyle factors this became 1.00 (95%CI: 0.97 to 1.03, p = 0.9). The 95% CI around this ratio indicates that an intervention which increased red cell folate by 100nmol/l would be unlikely to reduce the risk of incident symptoms by more than about 3%.

Table 4 shows hazard ratios for incident symptoms of depression over two years, comparing women with red cell folate levels in the bottom 10% with those in remaining 90%. Again, no association was found between incident depressive symptoms and baseline red cell folate (hazard ratios: unadjusted 1.30 (95% C.I. 0.93 – 1.83) and adjusted 1.22 (0.87 – 1.72)), although the wide confidence intervals reflect the fact that there were only 38 cases of depression in this group.

DISCUSSION

Principal findings

We found lower blood folate levels at baseline to be significantly associated with symptoms of anxiety and depression measured using the GHQ-12 in young women in Southampton. This relationship held after adjustment for possible confounding socio-economic and lifestyle factors, and is consistent with a recent systematic review showing a relationship between low folate levels and depression[14].

We found no relationship between baseline folate levels and incident symptoms of depression recorded in GP records over two years of follow-up. Our findings suggest

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therefore that lower blood folate is more likely to be a consequence of depression rather than a cause. This could result from reduced folate intake due to appetite loss associated with depression, confounded by increased smoking and alcohol consumption. This finding contradicts the previous prospective study carried out in Finland[13], but in our study we measured intracellular folate status directly rather than relying on estimates of folate intake, and this is the first prospective study of blood folate levels and depressive symptoms[14].

Strengths and weaknesses of the study in relation to previous research

Other strengths were that it was prospective, and involved a large number of participants shown to be representative of the general population of women of child-bearing age, who are at high risk of depression. We followed up 79% of participants, who were broadly representative of the whole sample. The Finnish study was based on hospital discharge records and included information on only 47 cases of depression among 2682 patients assessed at baseline[13].

As we excluded women with baseline caseness on the GHQ-12 and those with pre-existing depression in GP records, we could study purely incident depression, like the Finnish study[13]. Thus we distinguished possible risk factors for onset of depression from those linked with existing depression, or with an increased duration of depression, and thus with prevalence levels. Such distinctions are important in assessing causal relationships.

As in the Finnish study[13], a range of socio-economic and lifestyle variables were also measured at baseline, allowing us to determine relationships with blood folate levels after adjustment for possible confounders.

A possible weakness is that ‘cases’ of anxiety and depression at baseline were identified on the basis of scores on the GHQ-12, which is a screening instrument and not diagnostic. Ideally those scoring above the threshold for caseness should have undergone a second stage diagnostic interview or longer self-completed depression measure (as in the Finnish study[13]), but resources did not permit several hundred follow-up interviews or longer depression-specific measures. Nonetheless, a significant relationship was found with caseness on the GHQ-12, suggesting it was a good enough proxy measure of depression and sufficiently related to folate levels to confirm the findings of previous cross-sectional studies. Furthermore a strength of the GHQ-12 is that, although it is not specific for depression, it is highly sensitive and by removing all those with caseness at baseline we can be confident we removed almost all women with existing depression in order to study purely incident symptoms.

Another possible weakness is that we have information on incident depression only where symptoms were recorded in the GP records during follow-up, and no information on depression not presented to GPs. It is well established that GPs miss a significant proportion of cases of depression among patients attending their practices, at least when diagnosis is determined on a single occasion in cross-sectional studies[23]. However research shows that many of those cases undetected on a single occasion are subsequently picked up over the next few years[24], and those who are missed tend to be milder cases[25;26], suggesting GPs are better at diagnosing clinically significant depression than studies based on a single point in

time suggest. However, diagnostic interviews or longer depression-specific measures were not used to ascertain incident cases and we may have failed to identify some women with depression that remained undetected by the participating GPs. The Finnish study was based only on the extreme outcome of hospital admission for depression, and although the diagnoses were confirmed according to standardised psychiatric criteria, the study lacked any information on less severe incident depression among the rest of the cohort[13].

On the other hand we may have included some women whose symptoms were mild and did not represent clinically significant depression, although in 88% of cases the GP intervened with treatment or referral suggesting this is less likely. Any inaccuracy in case ascertainment would reduce the strength of potential associations with causal factors in the analysis, although we cannot see any reason why this would affect relationships with blood folate differentially.

The number of women who developed incident depressive symptoms was lower than the number with baseline symptoms and another possible explanation for our findings is the lower power of our study to examine associations with incident symptoms, although both the baseline sample and the proportion followed up were considerably larger than the one previous prospective study[13]. Levels of unemployment, perceived stress, and perceived financial strain were slightly lower among those followed up, and as these factors increase the risk of depression it may be that we missed relatively more cases among those for whom we have no follow-up data. We followed the women for two years, and may have failed to identify women who would become depressed in later years.

On the other hand, although we might have missed incident cases, there was no clear suggestion of a trend across all folate levels in the same direction as the relationship between low folate and baseline depression which if present would have supported the possibility of a type II error due to lack of power. We could not however exclude a clinically important causal effect among those with the lowest 10% of red cell folate levels, among whom the 95% CIs included a possible adjusted hazard ratio as high as 1.72, but the CIs were wide as this group included only 276 women.

Implications of our findings for policymakers

While lower red blood cell folate levels were significantly associated with prevalent symptoms of anxiety and depression, adjustment for socio-economic and lifestyle factors reduced the association significantly and there may be residual confounding that we are unable to account for. Therefore if low folate is an independent risk factor for depression, it seems to be a weak predictor and associated socio-economic risk factors are much more important according both to our data and previous studies[22;27]. We cannot exclude the possibility that very low levels of folate lead to subsequent symptoms of depression, but even if this is so our results suggest that the effect is relatively weak, and that significantly increasing blood folate levels through dietary folic acid supplementation at a population level would be likely to have only a small effect on the population risk of depression.

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The need for future research

This is only the second published longitudinal study of folate and depression[14], and further studies are needed before firmer conclusions can be drawn. Future studies should ideally include measurement of blood folate levels at baseline as in our study, and either psychiatric interviews or longer self-complete measures of depression both at baseline and follow-up.

Genetic epidemiology studies have shown that unipolar depression is associated with polymorphisms of the gene for the folate cycle enzyme methylenetetrahydrofolate reductase (MTHFR), along with bipolar disorder and schizophrenia[28]. It is possible that lower folate levels may be linked to depression only in the presence of these polymorphisms and not among the population as a whole. Characterisation of the MTHFR gene polymorphisms in future studies would allow the exploration of possible causal gene-environment interactions.

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WHAT IS ALREADY KNOWN ON THIS SUBJECT?

Lower blood folate levels have been associated with depression in cross-sectional surveys, but only one prospective study has been published, based on dietary intake rather than blood folate levels.

WHAT DOES THIS STUDY ADD?

Lower blood folate levels were associated with prevalent symptoms of anxiety and depression at baseline, in common with other cross-sectional surveys.

Lower folate levels were not however associated with subsequent depressive symptoms over two years of follow-up, suggesting that lower folate may be a consequence rather than a cause of depressive symptoms.

If low folate does predispose to depression, the effect is small compared with socio-economic factors and our findings do not support a policy of folic acid supplementation to prevent depression.

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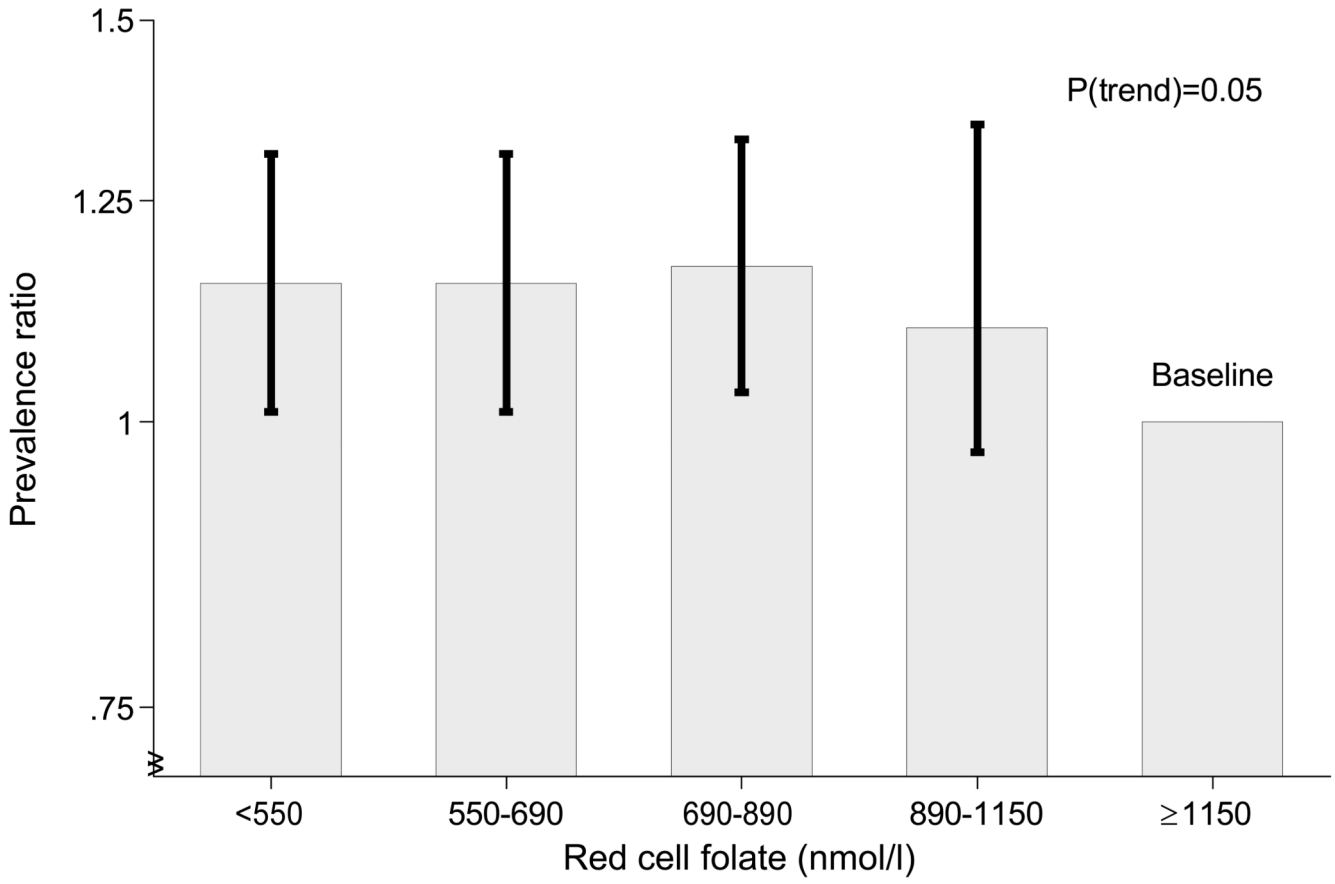

Figure 1. Adjusted prevalence ratios for case level symptoms of anxiety and depression on the GHQ-12 in relation to baseline red cell folate levels in five strata (adjusted for financial strain, exercise, and body mass index)

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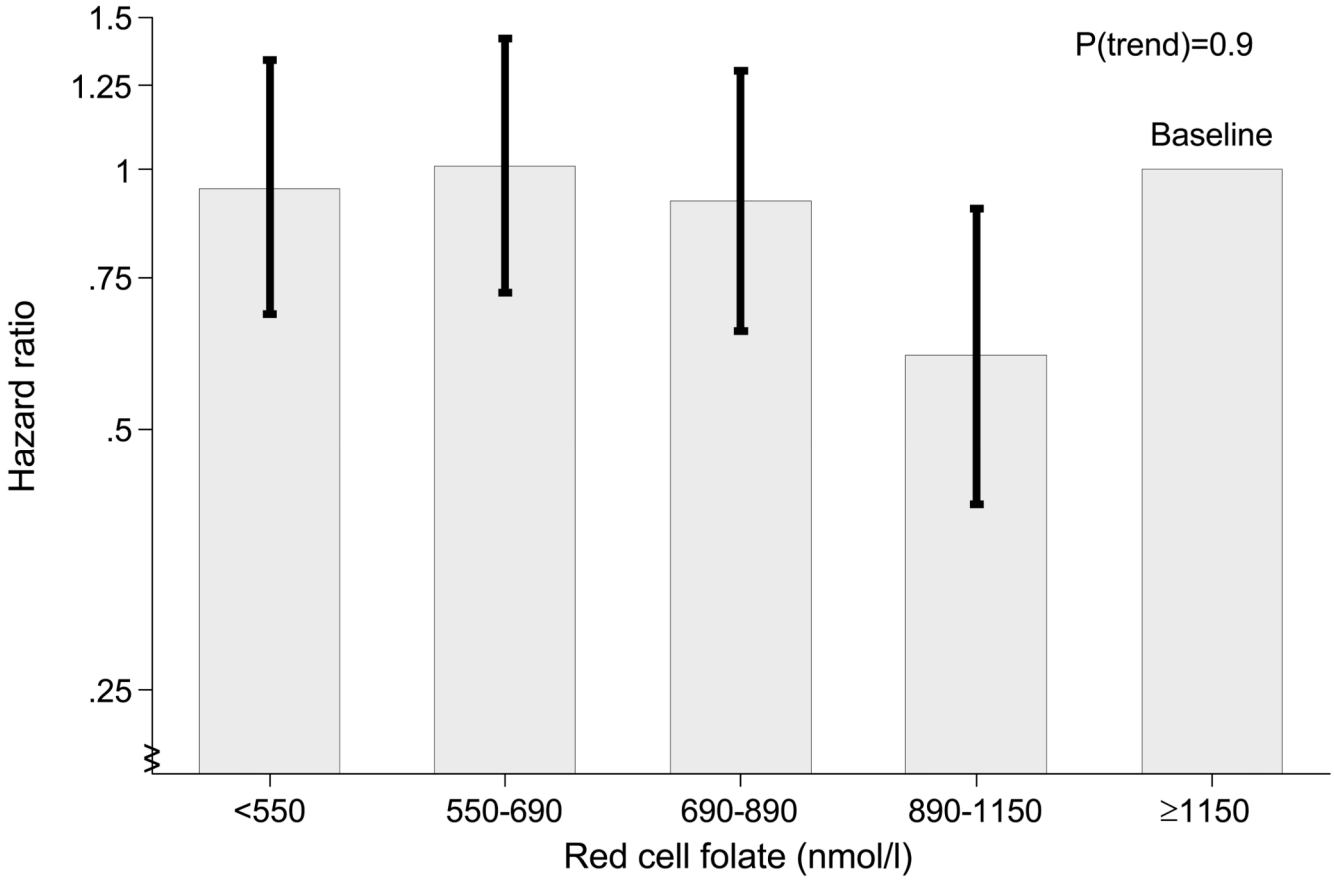

Figure 2. Adjusted hazard ratios for incident symptoms of depression in GP records over two years in relation to baseline red cell folate levels in five strata (adjusted for education, smoking, and receipt of benefits)

Table 1

Baseline data for all participants, those with red cell folate measurements, and those who were followed up over two years

Characteristic		Baseline (all participants) (n=7020)	Baseline (folate measured) (n=5051)	Followed-up (folate measured) (n=2732)
Mean age (years) at baseline (SD)		28.4 (4.2)	28.7 (4.1)	28.9 (4.1)
Age at baseline (years)	20-24	1743 (25%)	1101 (22%)	565 (21%)
	25-29	2401 (34%)	1727 (34%)	908 (33%)
	30-34	2876 (41%)	2223 (44%)	1259 (46%)
Strenuous exercise	No	2317 (33%)	1648 (33%)	833 (31%)
	Yes	4689 (67%)	3393 (67%)	1895 (69%)
Perceived stress	None	1555 (22%)	1136 (23%)	809 (30%)
	Slightly	2677 (38%)	1941 (38%)	1179 (43%)
	Moderately	1344 (19%)	966 (19%)	439 (16%)
	Quite a lot	1186 (17%)	825 (16%)	255 (9%)
	Extremely	250 (4%)	177 (4%)	46 (2%)
Employment status (working last week)	No	1609 (23%)	1140 (23%)	549 (20%)
	Yes	5409 (77%)	3910 (77%)	2183 (80%)
Qualification level	None	299 (4%)	190 (4%)	80 (3%)
	GCSE D-G	709 (10%)	523 (10%)	276 (10%)
	GCSE A*-C	1848 (26%)	1307 (26%)	738 (27%)
	A level	2261 (32%)	1611 (32%)	903 (33%)
	HND	381 (5%)	301 (6%)	169 (6%)
	Degree or above	1489 (21%)	1092 (22%)	550 (20%)
Receiving benefits	No	5926 (84%)	4284 (85%)	2379 (87%)
	Yes	1090 (16%)	765 (15%)	351 (13%)
Woman's own social class	I	264 (4%)	202 (4%)	118 (5%)
	II	2015 (32%)	1495 (33%)	797 (32%)
	IIIN	2545 (41%)	1816 (40%)	1020 (41%)
	IIIM	487 (8%)	359 (8%)	214 (9%)
	IV	845 (13%)	588 (13%)	295 (12%)
	V	125 (2%)	84 (2%)	43 (2%)
Perceived financial strain	Living comfortably	4258 (61%)	3103 (62%)	1883 (69%)
		2251 (32%)	1590 (32%)	765 (28%)
	Just about getting by Finding it difficult	502 (7%)	352 (7%)	83 (3%)
Currently smoking	No	4993 (71%)	3673 (73%)	2058 (75%)
	Yes	2022 (29%)	1375 (27%)	671 (25%)

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Characteristic		Baseline (all participants) (n=7020)	Baseline (folate measured) (n=5051)	Followed-up (folate measured) (n=2732)
Units of alcohol consumed per week Median (Inter Quartile Range)		4.7 (1.35-11.5)	4.7 (1.5-11.0)	4.6 (1.5-10.5)
Body mass index(kg/m^2) Median (IQR)		24.3 (21.9-27.8)	24.4 (22.1-27.9)	24.4 (22.1-27.8)
Body mass index (kg/m^2)	<20	606 (9%)	369 (7%)	187 (7%)
	20-24.9	3368 (49%)	2444 (49%)	1355 (50%)
	25-29.9	1827 (26%)	1354 (27%)	735 (27%)
	30-34.9	736 (11%)	550 (11%)	286 (11%)
	≥35	400 (6%)	296 (6%)	147 (5%)

Note: numbers do not always total to the full number in each group due to missing values.

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Table 2

Red cell folate in five groups and prevalence of case level symptoms of anxiety or depression on the GHQ-12 at baseline

Red cell folate level in five strata (nmol/l)	Prevalent case level symptoms (GHQ-12 score 3 or greater)		Unadjusted analysis		Adjusted analysis*	
	Number assessed	Number (%) with case level symptoms	Prevalence ratio	95% confidence interval	Prevalence ratio	95% confidence interval
<550	1029	343 (33%)	1.20	1.06-1.37	1.15	1.01-1.31
550-690	981	327 (33%)	1.20	1.05-1.38	1.15	1.01-1.31
690-890	1041	339 (33%)	1.18	1.03-1.34	1.17	1.03-1.33
890-1150	981	297 (30%)	1.09	0.95-1.26	1.10	0.96-1.25
≥1150	1019	282 (28%)	1.0	(baseline)	1.0	(baseline)
Total	5051	1588 (31)	P_{trend}= 0.005+		P_{trend}= 0.05+	

*Adjusted for perceived financial strain, exercise, and body mass index

+P_{trend} based on the continuous measure of red cell folate

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Table 3

Red cell folate in five groups and incident symptoms of depression in GP records over two years

Red cell folate level in five strata (nmol/l)	Incident depressive symptoms		Unadjusted analysis		Adjusted analysis*	
	Number assessed	Number (%) with symptoms	Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval
<550	544	69 (13%)	1.12	0.90-1.57	0.95	0.68-1.34
550-690	522	67 (13%)	1.12	0.80-1.58	1.01	0.72-1.42
690-890	557	64 (11%)	1.01	0.71-1.42	0.92	0.65-1.30
890-1150	532	40 (8%)	0.64	0.43-0.94	0.61	0.41-0.90
≥ 1150	577	67 (12%)	1.0	(baseline)	1.0	(baseline)
Total	2732	307 (11%)	P_{trend}= 0.4+		P_{trend}= 0.9+	

*Adjusted for education, smoking, and benefits

+P_{trend} based on the continuous measure of red cell folate

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Table 4

Lowest 10% of red cell folate levels and incident depressive symptoms in GP records over two years

Red cell folate level (nmol/l)	Incident depressive symptoms		Unadjusted analysis		Adjusted analysis*	
	Number assessed	Number (%) with symptoms	Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval
Lowest 10% (<468)	276	38 (14%)	1.30	0.93-1.83	1.22	0.87-1.72
Remaining 90%	2456	269 (11%)	1.0	(baseline)	1.0	(baseline)
Total	2732	307 (11%)				

*Adjusted for education, smoking, and benefits