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Short Communication

Associations of C-reactive protein and psychological distress are modified by antidepressants, supporting an inflammatory depression subtype: Findings from UKHLS

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ABSTRACT

Background: Clinical evidence increasingly suggests inflammation may be important specifically for an etiologically distinct depression subtype, characterised by resistance to antidepressant medication. However, epidemiological investigations of the relationship of inflammation with depression and psychological distress have failed to acknowledge these developments, which may have resulted in bias or masking of associations driven by the subtype. This may have contributed to inconsistent results in epidemiological studies, and equivocal support for an inflammation–depression link.

Methods: An antidepressant-resistant, inflammatory depression subtype would result in stronger associations of depressive symptomatology with inflammation among antidepressant users than non-users, due to over-representation of subtype individuals among antidepressant users experiencing severe or persistent symptoms. We investigate, in a sample of 10,363 UK adults aged 16–98, modification by antidepressants of cross-sectional and longitudinal associations between C-reactive protein and psychological distress (General Health Questionnaire score, GHQ). We account for confounding by age, gender, income, inflammatory somatic illness, body mass index and, in longitudinal models, baseline psychological distress. Sensitivity analyses consider smoking, ethnicity, and other medications.

Results: Robust associations of log-CRP and GHQ were seen for antidepressant users but not for non-users in both cross-sectional (coeff: 0.54, $p = 0.01$ vs 0.06, $p = 0.28$) and longitudinal models (coeff: 0.57, $p = 0.006$ vs 0.04, $p = 0.39$ two waves post-baseline). Cross-sectional associations were strongest for tricyclic users, and longitudinal associations strongest for SSRI users. In multilevel, repeated-measures longitudinal models, associations for antidepressant users peaked two waves after baseline before declining.

Conclusions: Results suggest evidence for existence of an inflammatory depression subtype. Previous studies' exclusion of antidepressant users and failure to consider interactive effects may have obscured associations driven by the subgroup. Follow-up work is now needed in community samples with clinical depression measures and prescription histories, to further elucidate the mechanisms involved.

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1. Introduction

Depression-like symptoms are produced by acute elevations in inflammatory activity, either as part of 'sickness behaviour' following infection or injury, or by experimentally-induced responses to exogenous inflammatory agents (Miller et al., 2009). The inflammatory theory of depression argues that, similarly, depressive symptoms and syndromes are linked to variations in endogenous 'systemic' inflammation, a milder analogue of the acute inflammatory response which occurs in the absence of infection or injury. In

large community samples this has been investigated by examining associations of circulating inflammatory markers with depression diagnoses or questionnaire-derived psychological distress, concurrently or after a follow-up period. However, both cross-sectional (Dowlati et al., 2010; de Menezes et al., 2017) and longitudinal community studies (Valkanova et al., 2013; Chocano-Bedoya et al., 2014; Au et al., 2015; Das, 2016) are equivocal in their support for an impact of inflammation on depressive symptomatology. Heterogeneity in results may partly relate to modifying factors such as age, gender and follow-up time (Das, 2016; Engler et al., 2016), but clinical work increasingly suggests systemic inflammation is important specifically for an etiologically distinct depressive subtype, characterised by poor antidepressant treatment response (Barnes et al., 2017). Non-response to antidepressants is predicted

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by circulating inflammatory markers (Eller et al., 2008), gene variants associated with elevated inflammation (Baune et al., 2010) and transcription of genes in the inflammatory cytokine pathway (Powell et al., 2013), while administration of anti-inflammatory agents improves treatment response (Raison et al., 2013). Thus, in epidemiological studies, mixed findings may relate to failure to consider a distinct inflammatory-depressive ‘immunophenotype’, which may obscure associations (Barnes et al., 2017). Meanwhile, antidepressants may partly work via anti-inflammatory actions, since they appear to have anti-inflammatory effects peripherally and within the brain (Tynan et al., 2012), but certain antidepressants may promote inflammation, with cross-sectional CRP elevations net of depressive symptoms reported for tricyclics, tetracyclics, and serotonin–norepinephrine reuptake inhibitors, but not SSRIs (Hamer et al., 2011; Vogelzangs et al., 2012).

The relationship between inflammation, depressive symptomatology and antidepressants is therefore complex, possibly modified further by antidepressant type. If an inflammatory-depressive subtype exists characterised by poor antidepressant response, in an observational study we should expect a stronger inflammation–depression relationship among antidepressant users compared to non-users, since individuals with inflammatory depression will be over-represented among users reporting severe or persistent symptoms. If antidepressants work via anti-inflammatory effects, we should expect a weaker relationship among users, as variation at the high end of the range for both inflammatory markers and depressive symptoms are reduced together, relative to depressed but medically untreated individuals. If certain antidepressants raise inflammatory markers while reducing depressive symptoms, we should expect weaker inflammation–depression links among users of those antidepressants specifically.

Epidemiological studies typically exclude antidepressant users (Camacho et al., 2014; Zalli et al., 2016), or adjust for antidepressants (Gimeno et al., 2009; Das, 2016). If antidepressant use modifies associations, exclusion will produce biased estimates, while adjustment without subgroup analysis may obscure associations concentrated in a small treatment-resistant subgroup. To our knowledge only one study has considered antidepressant modification, reporting a cross-sectional association of the inflammatory marker C-reactive protein (CRP) with somatic (but not cognitive) depressive symptoms restricted to non-users of antidepressants. The authors suggest this supports anti-inflammatory effects of antidepressants (White et al., 2016), but since participants with CRP values suggesting current infection were not excluded, associations may also reflect infection-related sickness behaviour, statistically detectable only in the larger group.

We integrate the hypothesis of the antidepressant-resistant, inflammatory depression subtype into an epidemiological study. We investigate modification of cross-sectional and longitudinal associations of CRP with General Health Questionnaire score, a measure of psychological distress, by all antidepressants, and by antidepressant types.

2. Methods

The UKHLS is an annual longitudinal survey of over UK 40,000 households, comprising a larger General Population Sample (GPS), a stratified clustered random sample of households representative of the UK population which joined in 2009–10, and a smaller component from the pre-existing British Household Panel Survey (BHPS) (Benzeval et al., 2014). Sociodemographic information was obtained at annual interviews, and biomedical measures taken during a nurse visit five months after the wave 2 interview (W2, GPS participants) or wave 3 interview (W3, BHPS participants). Respondents were eligible for a biomedical visit if they took

part in the corresponding main interview in English, were aged 16+, lived in England, Wales or Scotland, and were not pregnant. Of these 35875, 57.5% took part.

The initial sample was defined as participants present at the biomedical assessment and at least one subsequent wave. Participants were excluded if they had CRP > 10mg/L, usually assumed to reflect current infection (Pearson et al., 2003). Of these 19,107, 11767 (61.6%) had usable CRP measurements, with missingness largely due to non-consent for blood sampling. 348 were excluded for lacking any follow-up GHQ measurements, and 1056 for missing covariates, leaving 10,363.

3. Measures

CRP was analyzed from serum using the N Latex CRP mono Immunoassay on the Behring Nephelometer II Analyzer (Benzeval et al., 2014). Psychological distress was measured using the 12-item General Health Questionnaire (GHQ) (Goldberg et al., 1997). Participants were asked 12 questions to capture depressive and anxiety symptoms in the past four weeks, and an overall score (range 0–36) calculated.

All antidepressants with BNF codes 04.01.01–04.01.04 were considered, namely tricyclics, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and ‘other’ antidepressants (section 04.01.04). 958 participants were taking antidepressants, most commonly SSRIs (551 participants) followed by tricyclics (303 participants). 11 were taking MAOIs and 151 other antidepressants. 57 participants were taking two, usually a tricyclic plus SSRI (N = 38).

All models adjusted for age and gender at biomedical assessment, and age-band specific quartiles of equivalised household income from W2/W3. Diagnoses at baseline of inflammatory somatic illness (asthma, emphysema, chronic bronchitis, cancer, cardiac problems including high blood pressure) were derived using questionnaire information from UKHLS W1/W2 (GPS participants) or BHPS W18 and UKHLS W2 (BHPS participants). Full-adjusted longitudinal models also included baseline GHQ score and diagnoses of somatic conditions during follow-up, again using annual questionnaire information. Baseline BMI was calculated from height and weight measured by a nurse using a portable stadiometer and Tanita-BF522 digital floor scales, and classified as <18.5, 18.5–24.9, 25.0–29.9, and ≥30. Anti-inflammatory medications included non-steroidal anti-inflammatory medications (NSAIDs), statins, and corticosteroids.

4. Analysis

GHQ scores approximated a normal distribution so were included untransformed in linear regressions; CRP was skewed and therefore log-transformed. Relationships were examined separately by antidepressant use: non-users, all antidepressants, SSRIs, tricyclics, MAOIs and others, combined treatment. To construct trajectories of CRP–GHQ associations, GHQ scores 1, 2 and 3 waves post-baseline were modelled as functions of baseline log-CRP, using an interaction term between log-CRP and waves since baseline. A repeated-measures, multilevel panel data structure was used, with measurements 1, 2 and 3 waves later nested within individuals. Baseline covariates including baseline GHQ were treated as time-invariant, and new diagnoses during follow-up as time-varying. Unbalanced data was allowed, meaning participants were included even if not present at all outcome waves. All analyses used robust standard errors to account for survey effects.

Antidepressant use was considerably more common among female participants, and related to GHQ score. Thus, to ascertain whether antidepressant use itself modified associations, we

explored gender interaction, and reran models restricted to participants with clinically relevant GHQ scores following Goldberg (Goldberg et al., 1997), using both the ≥ 3 and ≥ 4 cutoffs from 0 to 12 scoring. Further sensitivity analyses adjusted for anti-inflammatory medications, time of day, season, and processing time of blood samples, and for smoking, which may be a cause or consequence of psychological distress (Taylor et al., 2014). A sensitivity analysis exploring impact of ethnicity excluded the 3.7% of participants defining not as a white group, while another excluded women taking oral contraceptives (OCs) or hormone replacement therapy (HRT) Table 1.

5. Results

Compared to non-users, antidepressant users were slightly older, less affluent and considerably more likely to be female. They were more likely to be white, current or former smokers, and to have extreme BMIs (underweight or obese). They were more likely to take anti-inflammatory medications, OCs or HRT, and have a relevant somatic illness. They had higher CRP and higher GHQ scores at all waves (all $p < 0.05$).

In cross-sectional models adjusted for age, gender and household income (Table 2), CRP was associated with GHQ for all participants. For non-users of antidepressants, adjustment for BMI and long-term illness explained associations. Conversely, a GHQ elevation for antidepressant users was robust (coeff: 0.54, $p = 0.01$) and strongest for tricyclic users (coeff: 1.07, $p = 0.006$). No significant associations were seen for other antidepressant types. There was

no significant CRP-GHQ association for participants not taking antidepressants with clinically significant GHQ symptoms using either the lower or the higher threshold (respectively, $N = 1816$, coeff: 0.04, $p = 0.76$; $N = 1423$, coeff: -0.02 , CI: $-0.28-0.24$, $p = 0.88$). In a whole-sample model, an interaction term for CRP*gender suggested a weaker CRP-GHQ association for women, but was non-significant (coeff = -0.18 , $p = 0.08$).

Adjustment for smoking made little difference (0.49, $p = 0.02$ for all antidepressant users; 1.01, $p = 0.01$ for tricyclics), as did adjustment for anti-inflammatory medications (0.53, $p = 0.001$ for all antidepressants, 1.06, $p = 0.007$ for tricyclics), or time of day, season and processing time of blood samples (0.53, $p = 0.01$ for all antidepressants; 1.06, $p = 0.007$ for tricyclics), excluding non-white/mixed participants (for all antidepressants, 0.58, $p = 0.007$; for tricyclics, 1.10, $p = 0.005$), or excluding women taking OCs/HRT (for all antidepressants, 0.52, $p = 0.02$, for tricyclics, 1.05, $p = 0.01$).

6. Longitudinal

In longitudinal models adjusted for baseline GHQ, age, gender, household income, a modest association emerged across the three years for non-users of antidepressants (coeff: 0.12, $p = 0.02$ at the third outcome point), which was explained by addition of BMI and long-term illness. Among users, there was no association one or three waves post-baseline, but a sharp peak in associations after two waves, robust to adjustment for BMI and illness (coeff: 0.57, $p = 0.006$). This was strongest for SSRI users (fully-adjusted

Table 1
Descriptive characteristics of analytic sample, by antidepressant use ($N = 10,363$).

		None N = 9405	Any N = 958	SSRIs ^a N = 508	Tricyclics N = 251	MAOIs ^b and others N = 142	Combined N = 57
BASELINE CHARACTERISTICS		Mean(S.D.)	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)
GHQ ^c		10.5(4.8)	15.6(7.4)	15.4(7.2)	14.2(6.8)	17.4(8.3)	19.3(7.4)
C-reactive protein		1.95(1.97)	2.65(2.32)	2.37(2.13)	2.99(2.44)	2.81(2.49)	3.21(2.69)
Age (years)		51.7 (16.9)	53.1 (14.2)	50.4 (13.8)	58.8 (14.2)	52.1(13.0)	53.6(13.1)
Gender		(%)	(%)	(%)	(%)	(%)	(%)
Male		46.6	25.9	23.2	27.9	31.0	28.1
Female		53.4	74.1	76.8	72.1	69.0	71.9
Equivalised household income quartiles (age-specific)							
Highest		26.7	19.0	19.3	19.5	16.2	21.1
3		26.2	25.2	24.8	27.1	25.4	19.3
2		24.9	26.3	27.0	24.3	27.5	26.3
Lowest		22.3	29.5	28.9	29.1	31.0	33.3
Ethnicity							
White		96.0	98.3	98.6	98.8	96.5	98.2
Other (incl. mixed)		4.0	1.7	1.4	1.2	3.5	1.8
Relevant somatic illness							
No		72.4	58.5	65.0	51.0	54.2	43.9
Yes		27.6	41.5	35.0	49.0	45.8	56.1
Smoking							
Never smoker		54.5	42.9	43.1	43.8	42.3	38.6
Ex-smoker		28.2	29.2	29.9	33.1	21.1	26.3
Current, ≤ 10 /day		9.0	11.0	12.2	8.4	10.6	12.3
Current, 11–20/day		7.1	12.9	11.2	11.6	19.7	17.5
Current, >20 /day		1.2	4.0	3.5	3.2	6.3	5.3
Body Mass Index (kg/m ²)							
18.5–24.9		29.6	22.7	23.2	18.7	26.8	24.6
25.0–29.9		39.9	31.9	32.3	35.5	27.5	24.6
30–34.9		19.2	23.4	22.8	26.3	20.4	22.8
>35		8.3	16.6	16.5	13.9	19.7	21.1
<18.5		3.1	5.4	5.1	5.6	5.6	7.0
NSAIDs ^d /statins/corticosteroids							
No		80.9	66.4	73.8	53.0	68.3	54.4
Yes		19.1	33.6	26.2	47.0	31.7	45.6
Oral Contraceptives /HRT							
No		94.5	92.8	92.7	94.4	90.9	91.2
Yes		5.5	7.2	7.3	5.6	9.2	8.8
FOLLOW-UP		Mean(S.D.)	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)	Mean(S.D.)
GHQ 1 wave later		10.4(4.9)	14.7(7.3)	14.6(7.2)	13.4(6.6)	16.1(8.1)	17.8(7.8)
GHQ 2 waves later		10.5(5.1)	14.6(7.3)	14.3(7.1)	13.1(6.2)	16.9(8.3)	18.5(7.7)
GHQ 3 waves later		10.6(5.2)	14.4(7.1)	14.2(6.8)	13.1(6.5)	15.8(8.2)	17.8(8.0)

^a Selective serotonin reuptake inhibitors.

^b Monoamine-oxidase inhibitors.

^c General Health Questionnaire Score.

^d Non-steroidal anti-inflammatory medications.

Table 2
Elevations in GHQ^a score per unit log-transformed baseline CRP, by antidepressant use.

CROSS-SECTIONAL ASSOCIATIONS ^c											
				Coeff	CI	P					
Non-users				0.13	0.03–0.23	0.01	Non-users				
All types				0.63	0.23–1.05	0.004	All types				
SSRIs ^b				0.41	–0.19–1.01	0.18	SSRIs				
Tricyclics				1.18	0.40–1.95	0.003	Tricyclics				
MAOIs ^c /Others				0.58	–0.46–1.62	0.28	MAOIs ^c /Others				
Combined				–0.37	–2.17–1.42	0.68	Combined				
*Adjusted for age, gender, household income						*Adjusted for age, gender, household income, long-term illness and BMI categories					
LONGITUDINAL ASSOCIATIONS											
Non-users		Waves later	Coeff	CI	P	Non-users		Waves later	Coeff	CI	P
		1	0.06	–0.03–0.15	0.22			1	0.02	–0.07–0.12	0.61
		2	0.09	–0.01–0.18	0.08			2	0.04	–0.06–0.14	0.39
		3	0.12	0.02–0.22	0.02			3	0.07	–0.04–0.18	0.21
All types		Waves later	Coeff	CI	P	All types		Waves later	Coeff	CI	P
		1	0.16	–0.24–0.57	0.43			1	0.12	–0.28–0.53	0.55
		2	0.63	0.22–1.04	<0.001			2	0.57	0.16–0.98	0.006
		3	0.09	–0.32–0.50	0.66			3	0.04	–0.36–0.45	0.84
SSRIs		Waves later	Coeff	CI	P	SSRIs		Waves later	Coeff	CI	P
		1	0.22	–0.37–0.81	0.47			1	0.17	–0.42–0.76	0.57
		2	0.84	0.27–1.41	<0.001			2	0.77	0.21–1.34	0.008
		3	0.03	–0.51–0.57	0.91			3	–0.03	–0.56–0.50	0.91
Tricyclics		Waves later	Coeff	CI	P	Tricyclics		Waves later	Coeff	CI	P
		1	0.00	–0.60–0.61	0.99			1	–0.02	–0.63–0.59	0.95
		2	0.16	–0.47–0.79	0.62			2	0.12	–0.51–0.74	0.72
		3	–0.20	–0.93–0.53	0.59			3	–0.24	–0.51–0.74	0.52
MAOIs ^c /Others		Waves later	Coeff	CI	P	MAOIs ^c /Others		Waves later	Coeff	CI	P
		1	0.26	–0.88–1.39	0.66			1	0.24	–0.88–1.36	0.67
		2	0.29	–0.85–1.43	0.62			2	0.27	–0.85–1.39	0.63
		3	0.62	–0.56–1.79	0.30			3	0.61	–0.56–1.77	0.31
Combined		Waves later	Coeff	CI	P	Combined		Waves later	Coeff	CI	P
		1	–0.27	–2.17–1.64	0.78			1	–0.30	–2.21–1.60	0.76
		2	1.65	–0.53–3.83	0.14			2	1.61	–0.60–3.83	0.15
		3	0.07	–1.98–2.13	0.94			3	0.07	–1.97–2.11	0.95
*Adjusted for baseline GHQ, age, gender, income						*Adjusted for baseline GHQ, age, gender, income, long-term illness, BMI					

^a General Health Questionnaire.

^b Selective serotonin reuptake inhibitors.

^c Monoamine-oxidase inhibitors.

coeff = 0.77, $p = 0.008$), and the small group using multiple antidepressants, although estimates for that group were imprecise (fully-adjusted coeff = 1.61, $p = 0.15$). The elevation was not explained by gender interaction (for men and women, elevations were 0.09, $p = 0.20$ and 0.13, 0.06 respectively; interaction $p = 0.65$).

Adjustment for smoking made little difference to year 2 elevations (0.54, $p = 0.009$ for all antidepressants; 0.74, $p = 0.01$ for SSRIs), as did adjustment for anti-inflammatory medications (0.56, $p = 0.007$ for all antidepressants; 0.77, $p = 0.008$ for SSRIs), or for time of day, season and processing time of blood samples (0.57, $p = 0.006$ for all antidepressants; 0.77, $p = 0.008$ for SSRIs), exclusion of non-white/mixed participants (0.56, $p = 0.007$, for all antidepressants; 0.76, $p = 0.001$, for SSRIs) and exclusion of women taking OCs/HRT (0.63, $p = 0.004$ for all antidepressants; 0.81, $p = 0.007$ for SSRIs).

7. Discussion

Results suggest evidence for existence of an antidepressant-resistant, inflammatory depression subtype. Cross-sectional associations were strongest for users of tricyclics, rather than SSRIs to which most clinical evidence for the subtype relates. However, tricyclics are not usually prescribed as a first-line antidepressant, and may have been prescribed because SSRIs were ineffective, thus acting as a better filter for the antidepressant-resistant subtype than SSRI use. Alternatively, since inflammatory resistance to tricyclics has not been studied as much as SSRI resistance, inflammatory activity may also predict non-response to tricyclics.

Trajectories of GHQ 1, 2 and 3 waves post-baseline indicate that the longitudinal relationship of CRP and psychological distress is also substantially modified by antidepressant use, in particular SSRIs, for which predictive effects of inflammatory activity on treatment response are well documented. Among non-users of antidepressants, that a modest emergent association across the three-year outcome period was largely explained by BMI and chronic illness may reflect confounding by these factors, or that adiposity and chronic illness are key upstream drivers of systemic inflammation which in turn leads to psychological distress.

The increase for antidepressant users in associations at year 2 is difficult to explain. Since we have no information on antidepressant use post-baseline, this may relate to treatment secession, changes in antidepressant dosage or type, or further deterioration in responsiveness. Similarly, decreased associations at year 3 could reflect improved symptom management by pharmaceutical or other means, or baseline inflammation becoming, over time, an increasingly weak proxy of current inflammation.

8. Strengths and limitations

Unlike previous studies, we used data from a nationally-representative sample across the whole adult age range, considered modification by several types of antidepressants, and investigated evolution of associations across a three-year outcome period. However, the GHQ measures psychological distress, and associations with diagnosed depression may differ. We do not know pre-

scription histories or why particular antidepressants were prescribed, limiting the conclusions which can be drawn.

9. Conclusion

This study finds a substantially stronger relationship among antidepressant users than non-users of an inflammatory marker with psychological distress. Cross-sectional observations were strongest for tricyclic users, and longitudinal associations by SSRI users, indicating the mechanisms involved may be sensitive to antidepressant type. Results indicate that researchers should be careful to treat antidepressant use appropriately in epidemiological studies of the inflammation-depression link, and may support existence of an aetiologically distinct, antidepressant-resistant, inflammatory depression subtype. Further work in community samples considering diagnosed depression and prescription histories is now needed to elucidate the mechanisms involved.

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