ORIGINAL RESEARCH

Association between asthma, corticosteroids and allostatic load biomarkers: a cross-sectional study

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ABSTRACT

Background Allostatic load, a measure of early ageing or 'wear and tear' from adapting to environmental challenges, has been suggested as a framework with which to understand the stress-related disruption of multiple biological systems which may be linked to asthma. Considering the socioeconomic context is also critical given asthma and allostatic overload are more common in lower socioeconomic groups.

Aims Estimate the relationship between allostatic load and its constituent biomarkers, asthma and corticosteroid prescribing while controlling for socioeconomic status.

Methods Data from *Understanding Society* (a nationally representative survey of UK community-dwelling adults) waves 1–3 (2009–2012) allowed the identification of a sex-specific risk profile across 12 biomarkers used to construct an Allostatic Load Index for a sample of 9816 adults. Regression analyses were used to examine the association of asthma status and corticosteroid prescriptions with allostatic load and its constituent biomarkers while controlling for socioeconomic status (n=9805).

Results Subjects with currently treated asthma and no corticosteroid prescription have an allostatic load 1.21 times higher than those without asthma (p<0.001). Asthmatic subjects in receipt of inhaled corticosteroids had an allostatic load, approximately 1.12 times higher than those without asthma (p<0.001). This association persisted in sensitivity analyses and appeared to be driven by an association with specific biomarkers (dehydroepiandrosterone-sulfate, waist-to-height ratio and C-reactive protein).

Conclusion Early ageing, in the form of a higher allostatic load, was present even in the mildest asthma group not receiving inhaled corticosteroids. Allostatic load is helpful in understanding the increased all-cause mortality and multimorbidity observed in asthma.

Key messages

What is the key question?

► What is the relationship between allostatic load (a measure of stress-related 'wear and tear'), its constituent biomarkers and asthma when adjusting for corticosteroid prescribing and socioeconomic status.

What is the bottom line?

► Participants with asthma demonstrate greater wear and tear than those without asthma; an individual in the mildest asthma group aged 52 years, without any corticosteroid prescription, had an allostatic load equivalent to a 60 years old without asthma.

Why read on?

► Allostatic load has been shown to predict the development of many stress-related diseases which overlap with asthma comorbidity and therefore understanding this stress-disease link is important for the management of asthma and in potentially reducing its lifetime burden.

INTRODUCTION

Asthma is a highly prevalent disease affecting over 300 million people worldwide.[1] It is associated with a significant economic burden,[2] which is greatest among those with severe disease and lower socioeconomic groups.[3 4] Asthma medications are a major contributor to this burden.[3 5] Corticosteroids (CS), a cornerstone of asthma treatment, have also been implicated in the presence of many comorbidities[6 7] and recent research examining the relationship between comorbidity and systemic CS (SCS) exposure suggests that their use may bring forward comorbidity to an earlier age.[8] Collectively, these studies are suggestive of a link between asthma, CS exposure and the age at which several illnesses manifest.

Allostatic load (AL) which refers to the cumulative 'wear and tear' on the body as a result of regular and/or sustained activation of physiological systems in response to environmental challenges[9] can also be thought of in terms of premature ageing.[10] Like asthma, high AL has been linked to socioeconomic status (SES) as well as minority status.[11 12] It has been proposed as a potential framework with which to understand stress-related disruptions to multiple biological systems which may be linked to asthma[13] and more broadly as a potential means of redefining 'health' to focus on an individual's ability to adapt and self-manage.[14]

Psychological stress has been associated with both exacerbation risk and development of asthma via disruption to immune, endocrine or other biological systems.[15 16] An operationalisation of AL to capture potential stress-related dysregulation across multiple systems may be useful in understanding comorbidity accumulation as well as the development of asthma. However, these relationships are likely to be complex, and are further complicated as CS are used to treat asthma and the physiological response to stress causes the release of endogenous glucocorticoids. Similarly, lower SES is associated with an increased AL[17] and within high-income

countries like the UK is generally associated with greater asthma prevalence and burden.[18] To our knowledge, only one study has examined the link between asthma and AL.[19] While this study demonstrated an association, it was in a small cohort of children and adolescents in Canada, where changes in endogenous sex hormones may complicate the relationship between AL and asthma given sex differences in asthma prevalence at different ages.[20]

Understanding the relationship between AL, asthma and CS may potentially be relevant to a holistic approach to asthma management, for example, using adaptive self-management techniques to reduce AL and the risk of stress-related disease. Indices of AL may also provide a useful metric with which to identify at risk individuals earlier, potentially delaying entry into the disease span of their life course, or in identifying biomarkers which may offer research pathways to better understand the role of stress in asthma. The objectives of this paper were to examine the association between AL and asthma apart from CS prescriptions and holding SES constant in an adult population and to examine these associations for individual AL biomarkers.

METHODS

Data

Data on adults aged 16 and over were taken from waves 1 to 3 (2009–2012) of the *Understanding Society* survey,[21] a large nationally representative sample of the UK population. Documentation describing the full data collection process is available elsewhere.[22] While *Understanding Society* is a panel survey, the data used here consist of two pooled cross-sectional waves where a nurse collected blood samples among other physiological measures from respondents.[23] Apart from nurse health assessment data, which was used to construct the AL Index (see next), all other data were self-reported. As this research was based on secondary analysis of primary data for which ethical approval had been previously obtained, no additional ethical approval was required and it was done without public/patient involvement. This database may be shared on request to the UK Data Service (https://www.ukdataservice.ac.uk/).

Allostatic Load Index

To maintain consistency with previous work using this dataset,[11] we used 12 biomarkers to construct an AL Index: creatinine clearance rate, insulin-like growth factor one (IGF1), dehydroepiandrosterone-sulfate (DHEA-s), clauss fibrinogen, glycated haemoglobin, pulse, systolic and diastolic blood pressures, C-reactive protein (CRP), ratio of total to high-density lipoprotein (HDL) cholesterol, triglycerides and waist-to-height ratio (W2H). A binary variable was used to identify whether an individual was in the high-risk quartile for each biomarker in the *Understanding Society* data. As it is recognised that the distribution of AL biomarkers is consistently different between males and females the identification of a high-risk quartile was sex-specific. Increasing levels represented higher risk for all biomarkers except IGF1, DHEA-s and creatinine clearance rate. These were summed to create an AL Index ranging from 0 to 12. While this specification of AL can make comparisons across studies difficult as the high-risk quartile is identified within the sample under observation, the approach has consistently been found to predict health and mortality[24] while potentially offering a clearer link to SES over other suggested measures of early ageing.[17]

Asthma and asthma medication

In wave 1, individuals were asked if they had physician diagnosed asthma and in subsequent waves whether they still had or had been newly diagnosed with this condition.[21] Individuals who reported having asthma in wave 1 but did not report a change in asthma status in subsequent waves were assumed to still have asthma. During the nurse visit, individuals were asked if they were 'taking or using any medicines, pills, syrups, ointments, puffers or injections prescribed for you by a doctor or a nurse?' which were coded using the British National Formulary (BNF).[25] A separate question asking whether each medication was taken/used in the last 7 days was used in sensitivity analysis. Under a special end-user licence, it was possible to identify those in receipt of inhaled CS (ICS), SCS as well as other respiratory medications (eg, Short Acting Beta-Agonist) based on BNF codes and descriptions.[23] A variable was created to broadly align with the Global Initiative for Asthma (GINA) treatment strategy guidelines[26]: (1) no asthma diagnosis and no prescription for any CS (control group); (2) self-reported physician diagnosed asthma and in receipt of respiratory medication (henceforth currently treated (CT) asthma) but no ICS and no SCS prescription; (3) CT asthma, ICS prescription but no SCS prescription; (4) CT asthma and SCS prescription (see online supplementary figure E1).

Statistical methods

To control for confounding between SES and asthma, information was included on an individual's age (and age-squared), sex, log of equivalised household income,[27] employment status, highest educational achievement, urban/rural dwelling status, self-reported ethnicity (any white background vs other), marital status and whether the individual is responsible for children under 18 years. Sample means and proportions were estimated on the main variables. While not included in the regression due to issues of collinearity and missing observations, percent predicted FEV_1 was used to examine lung function across CT asthma/CS groups. Given the small numbers of individuals in group 4 (n=11), inference related to this group would be troublesome and this group was excluded from the analysis.

Adjusting for confounders, regression models were used to examine the relationship between asthma and the AL Index (negative binomial regression with constant dispersion) and with high-risk status for each individual biomarker (logistic regression). Results in the main text are presented without (model 1) and with (model 2) adjustment for background SES. All analyses were conducted using Stata V.14.[28]

Sensitivity analyses including W2H as a confounder rather than a component of the AL Index, whether each medication was taken in the last 7 days, adjusting for other non-respiratory medication, restricting each AL biomarker cut-off to the high-risk quintile rather than quartile, using survey weights to examine whether results were biased by the sampling strategy or missing biomarker data, modelling age as a categorical variable (see table 1), using age to reflect the exposure window rather than as a covariate, and the inclusion of additional lifestyle variables, such as smoking history, for a subset of the sample are reported in the online supplement (in spite of the large sample size available for analysis, given the imbalance in the number of individuals across asthma groups we tested models using penalised maximum likelihood methods to ensure that bias was not present in the smaller numbers of individuals with asthma. Although not presented here, there was no difference in models

Table 1 Socioeconomic and Allostatic Load (AL) Index breakdown for the final sample used for analysis according to asthma/corticosteroids (CS) prescribing with t-tests for differences in sample characteristics relative to group 1 (control)

	1. No asthma/no CS prescriptions	2. Currently treated (CT) asthma/no ICS/no SCS	P value	3. CT asthma/ICS/ No SCS	P value	Total
Age (years), mean (SD)	52.4 (16.4)	52.2 (17)	0.894	55.1 (15.7)	0.002	52.5 (16.4)
Female, n (%)	5056 (54.8)	136 (68.7)	<0.001	250 (64.4)	<0.001	5442 (55.5)
Equivalised household income per person/month (£GBP), mean (SD)	2231 (1723)	2065 (1734)	0.180	1995 (1624)	0.008	2219 (1720)
Highest level of education, n (%)						
Degree	1985 (21.5)	42 (21.2)	0.914	73 (18.8)	0.201	2100 (21.4)
Other higher degree	1217 (13.2)	23 (11.6)	0.514	51 (13.1)	0.974	1291 (13.2)
A-level, etc.	1811 (19.6)	38 (19.2)	0.874	61 (15.7)	0.056	1910 (19.5)
GCSE, etc.	1923 (20.9)	29 (14.6)	0.033	83 (21.4)	0.800	2035 (20.8)
Other qualification	1014 (11)	24 (12.1)	0.618	46 (11.9)	0.598	1084 (11.1)
No qualification	1269 (13.8)	42 (21.2)	0.003	74 (19.1)	0.003	1385 (14.1)
Self-reported white ethnicity, n (%)	8801 (95.5)	192 (97)	0.313	373 (96.1)	0.534	9366 (95.5)
Employment status, n (%)						
Employed	4560 (49.5)	82 (41.4)	0.025	163 (42)	0.004	4805 (49)
Family care	456 (4.9)	13 (6.6)	0.300	17 (4.4)	0.614	486 (5)
Other, for example, long-term sickness	305 (3.3)	21 (10.6)	<0.001	36 (9.3)	<0.001	362 (3.7)
Retired	2626 (28.5)	56 (28.3)	0.950	134 (34.5)	0.010	2816 (28.7)
Self-employed	740 (8)	8 (4)	0.040	15 (3.9)	0.003	763 (7.8)
Full-time student	202 (2.2)	8 (4)	0.081	5 (1.3)	0.230	215 (2.2)
Unemployed	330 (3.6)	10 (5.1)	0.272	18 (4.6)	0.274	358 (3.7)
Urban, n (%)	6802 (73.8)	150 (75.8)	0.532	307 (79.1)	0.019	7259 (74)
Marital status, n (%)						
Divorced	1037 (11.2)	28 (14.1)	0.204	61 (15.7)	0.007	1126 (11.5)
Partner	5438 (59)	107 (54)	0.162	212 (54.6)	0.088	5757 (58.7)
Separated	186 (2)	3 (1.5)	0.618	9 (2.3)	0.679	198 (2)
Single	1873 (20.3)	41 (20.7)	0.893	61 (15.7)	0.027	1975 (20.1)
Widowed	685 (7.4)	19 (9.6)	0.252	45 (11.6)	0.002	749 (7.6)
Responsible for children under 18 years, n (%)	1742 (18.9)	42 (21.2)	0.411	76 (19.6)	0.733	1860 (19)
AL Index, mean (SD)	2.9 (2.2)	3.6 (2.3)	<0.001	3.6 (2.5)	<0.001	3 (2.3)
N =	9219	198		388		9805

CT asthma refers to those with a physician-diagnosed asthma and in receipt of any respiratory medication. Education achievement reflects the UK educational system, whereby degree/other higher degree would reflect approximately 17 years of education, A-level approximately 14 years and GCSE or no-qualification approximately 12 years or less.
GCSE, General Certificate of Secondary Education; ICS, inhaled corticosteroids; SCS, systemic corticosteroids.

accounting for this potential bias. Results can be made available on request).

RESULTS

The summary data for the study cohort of 9816 subjects used in the analysis are shown on table 1 (the steps used in preparing the final dataset from the survey is shown in the online supplementary figure E1). Of those with CT asthma (groups 2–4, n=597) approximately 33% (198/597) had no ICS or SCS prescriptions (group 2), 65% (388/597) had a prescription of ICS but no SCS (group 3) and 1.8% (11/597) had a prescription of SCS (group 4). Group 4 was not included in the analysis due to small numbers; however, it is worth highlighting that this group had the highest mean AL Index 5.2 (CI 3.8 to 6.6) while groups 1, 2 and 3 had mean AL indices of 2.9 (CI 2.9 to 3.0), 3.6 (3.3 to 3.9) and 3.6 (3.3 to 3.8), respectively. Along with a significantly higher AL relative to group 1 ($p<0.01$), groups 2 and 3 were also more likely to be female, have no educational qualification and fall into the 'Other' employment category. Those in group 3 were more likely to be divorced or widowed and less likely to be employed or self-employed relative to group 1. The pattern of medication use in asthma seen here is broadly consistent with other UK-based research using GINA guidelines on large administrative health records.[29] Although per cent predicted FEV_1 was not available for all subjects, consistent with expectation it declined across groups 1–4 with estimates of 94% (n=6093, CI 93.5 to 94.3), 84% (n=146, CI 77.2 to 89.9), 81% (n=272, CI 78.3 to 82.9) and 67% (n=7, CI 51.1 to 82.2), respectively. The mean age of the sample was 52.5 years and 56% were female.

Table 2 outlines the relationship between CT asthma/CS prescribing and the AL Index without (model 1) and with (model 2) adjustment for SES variables. Regardless of CS prescribing, those with CT asthma (groups 2–3) have a higher AL than those without physician-diagnosed asthma and no CS prescription (group 1). In model 1, those with CT asthma and no CS prescription (group 2) have an AL Index 1.26 times higher than those in

Table 2 Relationship between asthma/corticosteroids (CS) prescriptions and the Allostatic Load Index (incident rate ratio (IRR)) adjusted for socioeconomic factors and CS use

	Model 1	Model 2
Base: 1. No asthma/no CS prescriptions	IRR/(95% CI)	IRR/(95% CI)
2.Currently treated (CT) asthma/no ICS/no SCS	1.256*** (1.14 to 1.38)	1.205*** (1.12 to 1.30)
3.CT asthma/ICS/no SCS	1.229*** (1.14 to 1.32)	1.119*** (1.06 to 1.19)
N	9805	9805
Prob>F	<0.001	<0.001

Model 2 adjusts for age, age-squared, sex, equivalised household income, employment status, highest educational achievement, urban/rural dwelling status, whether the individual documented their ethnicity as white versus other, marital status and whether the individual is responsible for children under 18 years.
*Significant at p<0.05, **sig. at p<0.01, ***sig. at p<0.001.
ICS, inhaled corticosteroids; SCS, systemic corticosteroids.

group 1 (p<0.001). Those with CT asthma, an ICS prescription and no SCS prescription (group 3) have an AL Index 1.23 times higher than those in group 1 (p<0.001).

Following the inclusion of SES variables in model 2, the magnitude of these associations is reduced (table 2) though the pattern remains whereby those in group 2 (CT asthma/no ICS/no SCS) have an AL Index 1.21 times that of group 1 (p<0.001) while those in group 3 (CT asthma/ICS/no SCS) have an AL Index 1.12 times higher than those in group 1 (p<0.001). Full tables are available in the online supplement which also demonstrate a clear socioeconomic and age gradient: younger individuals, and those with higher educational achievement or higher income have a significantly lower AL Index (p<0.001).

To put this in perspective, consider an individual of average age in the sample (52.5 years). Based on the results from model 2, a 1 year increase in their age is associated with a 0.07 unit increase in their AL Index, *ceteris paribus*. Having CT asthma with no CS prescription (group 2 relative to group 1) is associated with 0.59 unit increase in their AL Index, *ceteris paribus*. Thus, in terms of its effect on AL, being in the mildest asthma group without any CS prescription relative to the control group is approximately equivalent to a penalty of 8 years on one's chronological age (0.59/0.07; note that because age squared was included in model 2 this estimate may vary slightly if using a reference age other than the mean age of the sample).

Figure 1 (and online supplementary table E8) present the odds of being in the high-risk quartile across each AL biomarker according to CT asthma/CS prescribing while adjusting for SES. A clear signal is seen across both groups for three biomarkers: CRP, W2H and DHEA-s. CT asthma subjects with and without ICS prescription had significantly greater odds of being in the high-risk quartile for these biomarkers.

Asthmatic subjects with an ICS prescription (group 3) had higher odds of being in the high-risk quartile for CRP (OR: 1.27, p=0.033), W2H (1.5, p<0.001) and DHEA-s (2.13, p<0.001) though not as high as asthmatic subjects without a CS prescription (group 2) relative to the control with ORs of 1.75 (p<0.001), 1.92 (p<0.001) and 2.18 (p<0.001), respectively. Similar to the results from table 2, the associations noted between groups 2 and 1 and between groups 3 and 1 were not however significantly different from each other. Additionally relative to group 1 those in group 3 have greater odds of being in the high-risk quartile for clauss fibrinogen (p<0.001) and those in group 2 have greater odds for pulse (p=0.016).

Estimates to the right of the black line represent an increase in the odds of being in the high-risk quartile though the high-risk quartile does not necessarily mean elevated levels; see the Allostatic Load Index section for individual biomarker configuration. Each model adjusts for age, age-squared, sex, equivalised household income, employment status, highest educational achievement, urban/rural dwelling status, whether the individual

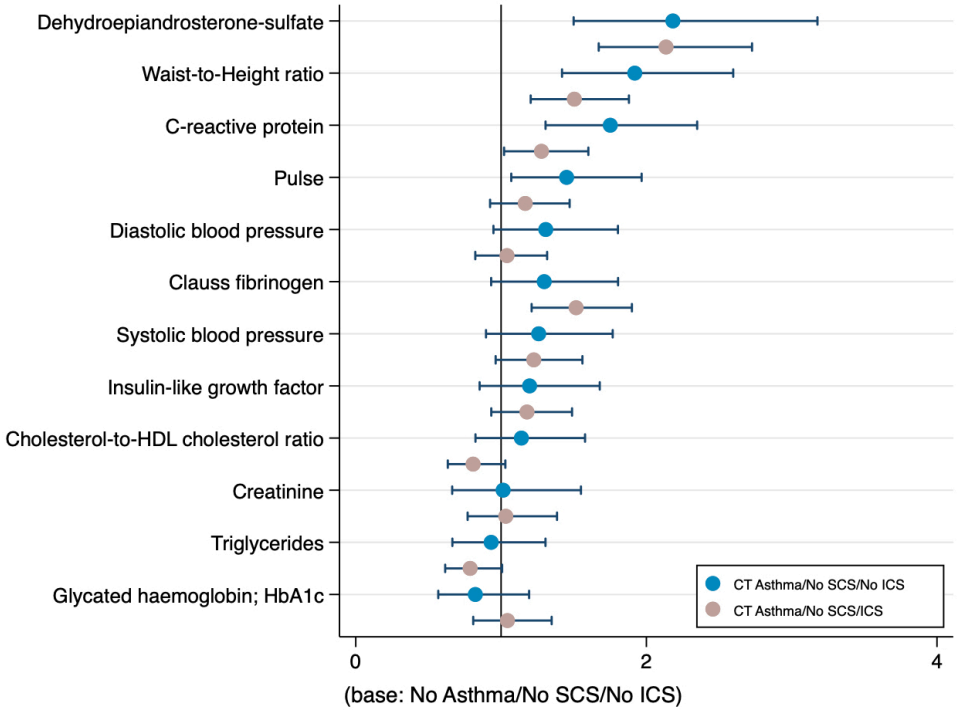

Figure 1 Relationship between asthma/corticosteroids (CS) prescription and the Allostatic Load Index biomarkers (ORs) adjusted for socioeconomic status (n=9805). CT, currently treated; ICS, inhaled CS; SCS, systemic CS.

documented their ethnicity as white, marital status and whether the individual was responsible for children under 18 years.

In sensitivity analyses of the relationship between CT asthma/CS prescribing and the AL Index, other potentially confounding factors were considered (see online supplementary table E1–E7). These additional analyses did not materially impact the incidence rate ratios reported in model 2 of table 2. In sensitivity analyses exploring the relationship between CT asthma/CS prescribing and individual AL biomarkers (see online supplementary table E8–E10), while adiposity and lifestyle factors, such as exercise and alcohol intake, explained in part the association between DHEA-s, CRP and CT asthma/CS prescribing they did not fully explain differences observed between these groups.

DISCUSSION

Our analyses show that, after adjusting for SES, those with CT asthma (self-reported physician-diagnosed asthma and in receipt of respiratory medication), but no CS treatment (ICS or SCS prescription) have an AL Index 1.21 ($p<0.001$) times higher than subjects with no asthma diagnosis. Those with CT asthma and an ICS prescription had an AL Index 1.12 ($p<0.001$) times higher than non-ashma controls. Taken together, these results suggest that the association between AL and asthma is not due to CS exposure and this association was supported in sensitivity analyses. In clinical terms, this suggests that subjects with physician-diagnosed CT mild asthma exhibit greater wear and tear than non-asthmatics which is independent of age, sex, SES and CS use.

The relevance of an elevated AL Index has been examined in a number of studies linking it with an increase in all-cause and disease-specific mortality risk for a given interval when adjusting for age, sex and other confounding factors.[30] Some caution is warranted when drawing inferences across studies as the biomarkers used to measure AL and the threshold defined as 'high-risk' often vary.[31] The wear and tear observed in our results may help explain the increased all-cause mortality observed among those with asthma.[32] Importantly, our results suggest that even mild asthma is equivalent in terms of the AL impact, of ageing by approximately 8 years, that is, those aged 52 with CT asthma and no CS have an equivalent AL to those aged 60 without asthma. The equivalent impacts of AL, with respect to the other degrees of asthma severity, are biologically plausible, specifically treatment of asthma with ICS potentially reducing the impact on AL. Programmes which help patient's adapt to life's challenges, including those related to the experience of illness, may be important alongside usual therapies in reducing patient's stress[33] and potential downstream morbidity.

The concept that ICS may have a potentially beneficial effect in terms of AL, through a wider anti-inflammatory effect, is supported by the fact that while CRP (a marker of inflammation) was higher in general among CT asthma subjects, those without a CS prescription (group 2) had relatively higher odds of being in the high-risk quartile for CRP than those with an ICS prescription (group 3); this observation has been noted elsewhere.[34] This would support a beneficial effect of ICS treatment in offsetting the increased AL associated with having asthma. The association between CT asthma and CRP was attenuated when adjusting for W2H suggesting that part of this relationship is mediated by adiposity. In addition, compared with group 1, risk levels for other metabolic biomarkers, such as triglycerides and total to HDL cholesterol, were also lower in group 3 compared with group 2 (although not significantly) which may also support this observation.

A consistent association was also observed across CT asthma groups and another AL biomarker, DHEA-s. When adjusting for SES, CT asthma subjects with and without CS prescription were twice as likely to be in the high-risk quartile for this biomarker compared with those without asthma or CS prescription. In the case of DHEA-s, 'high-risk quartile' refers to the quartile with the lowest recorded levels. Beneficial effects of sex hormones, such as DHEA-s, have been noted in asthma symptom control among adolescents[35] and the potential usefulness of DHEA-s has been described in screening for side-effects of CS exposure, as a CS-sparing alternative in treating conditions such as asthma or as a way of attenuating insensitivity to CS therapy in those who develop CS resistance.[36 37]

There are a number of limitations to this study. One limitation is that the analysis is cross sectional and therefore it was not possible to determine whether asthma leads to AL, whether the reverse is true or perhaps more likely that feedback exists between the two which intersects with an individual's genetic risk as well as the conditions and experiences of one's life. There is a suggestion that exposure to stress may alter immune function and therefore lead to the development of asthma or worsening asthma symptoms.[15 16] However, the humanistic burden of asthma on individuals is also well documented[38 39] and may plausibly result in a raised AL. Longitudinal analyses would help to shed light on this issue given we have shown evidence here to support a stress-disease link which is dissociated from CS use.

In the only prior study of AL and asthma, Bahreinian *et al* found that, in a longitudinal analysis of preadolescents, boys with a higher AL were more likely to be diagnosed with asthma 2 years later but found no such relationship in girls.[19] We did not find that the relationship between AL and asthma/CS prescribing was sex specific in a larger cross-sectional adult sample. Surprisingly, the Bahrenian adolescent study found no link between DHEA-s and asthma, though this may be due to the study population, given that DHEA-s production is linked to the onset of adrenarche[40] and the noted sex switch in asthma prevalence during this period.[20] However, in the Bahrenian study, sample size was small (n=352), the age-group studied was hormonally variable due to pubertal status, AL was measured differently and CS prescribing was not considered which makes study results difficult to compare.

A second limitation is that identifying the number or dosage of individual prescriptions was not possible, nor was determining how long an individual had been prescribed CS. This granularity around CS exposure may be reflected in their AL given previous research linking CS dose and duration to differential morbidity.[7 8] Furthermore it was not possible to measure medication adherence and only possible to identify individuals in receipt of CS prescription at the time of the nurse visit and not whether they were taking it as prescribed. However, the observed associations remain unchanged when restricting the analysis to those who reported taking their medication in the last 7 days which adds robustness around current medication adherence. It is also possible that some unobserved confounding remains, for example, asthma prevalence and higher AL may both be influenced by environmental exposures, such as air pollution. However, the associations between asthma and AL remain robust despite adjustment for urban dwelling and SES.

Additionally, data taken from the mainstage survey, including physician-diagnosed asthma, was self-reported which is a potential limitation; however, the large sample size available for analysis reduces the likelihood of this having a meaningful impact on the results presented here. Finally, the identification of a high-risk quartile is dependent on the data and may differ for

different samples while also not reflecting a meaningful clinical outcome. However, these data are from a large representative UK sample which allows control for socioeconomic confounders and provides strong support for an association between AL and asthma.

CONCLUSION

AL, as a measure of early ageing, provides a useful framework for understanding asthma and CS-induced morbidity especially given previous evidence of potential early expression of morbidity in patients with severe refractory asthma.[8] A lack of consistency in the use of biomarkers used to construct an AL Index has been documented elsewhere[31] which highlights the importance of including a breakdown of the association with individual biomarkers alongside a composite AL Index. Even subjects with mild asthma group (no CS prescription) have a significantly higher AL than those without asthma. Certain constituent biomarkers of AL are strongly positively associated with CT asthma although there is some evidence of a protective effect on AL for those in receipt of ICS.

While we cannot infer a causal association between asthma and raised AL, there does appear to be a stress-disease link that is not explained by iatrogenic effects. Prospective studies may allow a better understanding of the direction of causation across the life course including exploration of other modifying effects, such as the effect of smoking on the relationship between AL and asthma. The results presented in this paper shed new light on the mechanism by which asthma and asthma management may relate to comorbidity accumulation and may have implications for disease measurement and management.

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Patient and public involvement statement As this research was based on secondary analysis of a large national primary database, it was done without public/patient involvement.

Patient consent for publication Not required.

Ethics approval The University of Essex Ethics Committee has approved all data collection on Understanding Society main study and innovation panel waves, including asking consent for all data linkages except to health records. Requesting consent for health record linkage was approved at Wave 1 by the National Research Ethics Service (NRES) Oxfordshire REC A (08/H0604/124), at BHPS Wave 18 by the NRES Royal Free Hospital & Medical School (08/H0720/60) and at Wave 4 by NRES Southampton REC A (11/SC/0274). Approval for the collection of biosocial data by trained nurses in Waves 2 and 3 of the main survey was obtained from the National Research Ethics Service (Understanding Society—UK Household Longitudinal Study: A Biosocial Component, Oxfordshire A REC, Reference: 10/H0604/2).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. This database may be shared upon request to the UK Data Service (https://www.ukdataservice.ac.uk/).

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REFERENCES

1 Global Asthma Network. *The global asthma report*. Auckland, New Zealand, 2014.
2 Mukherjee M, Stoddart A, Gupta RP, *et al*. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med* 2016;14:113.
3 Barry LE, Sweeney J, O'Neill C, *et al*. The cost of systemic corticosteroid-induced morbidity in severe asthma: a health economic analysis. *Respir Res* 2017;18:129.
4 Chen W, Lynd LD, FitzGerald JM, *et al*. Influences of socioeconomic status on costs of asthma under universal health coverage. *Med Care* 2016;54:789–95.
5 O'Neill S, Sweeney J, Patterson CC, *et al*. The cost of treating severe refractory asthma in the UK: an economic analysis from the British thoracic Society difficult asthma registry. *Thorax* 2015;70:376–8.
6 Sweeney J, Patterson CC, Menzies-Gow A, *et al*. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the optimum patient care research database and the British thoracic difficult asthma registry. *Thorax* 2016;71:339–46.
7 Voorham J, Xu X, Price DB, *et al*. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. *Allergy* 2019;74:273–83.
8 Barry LE, O'Neill C, Patterson C, *et al*. Age and sex associations with systemic corticosteroid-induced morbidity in asthma. *J Allergy Clin Immunol Pract* 2018;6:2014–23.
9 McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. elaborating and testing the concepts of allostasis and allostatic load. *Ann N Y Acad Sci* 1999;896:30–47.
10 Castagné R, Garès V, Karimi M, *et al*. Allostatic load and subsequent all-cause mortality: which biological markers drive the relationship? findings from a UK birth cohort. *Eur J Epidemiol* 2018;33:441–58.
11 Chandola T, Zhang N. Re-Employment, job quality, health and allostatic load biomarkers: prospective evidence from the UK household longitudinal study. *Int J Epidemiol* 2018;47:47–57.
12 Seeman T, Merkin SS, Crimmins E, *et al*. Education, income and ethnic differences in cumulative biological risk profiles in a national sample of US adults: NHANES III (1988-1994). *Soc Sci Med* 2008;66:72–87.
13 Wright RJ, Schreier HMC. Seeking an integrated approach to assessing stress mechanisms related to asthma. *Am J Respir Crit Care Med* 2013;187:115–6.
14 Huber M, Knottnerus JA, Green L, *et al*. How should we define health? *BMJ* 2011;343:d4163.
15 Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. *Brain Behav Immun* 2007;21:993–9.
16 Wright RJ. Epidemiology of stress and asthma: from constricting communities and fragile families to epigenetics. *Immunol Allergy Clin North Am* 2011;31:19–39.
17 McCrory C, Fiorito G, Ni Cheallaigh C, *et al*. How does socio-economic position (SEP) get biologically embedded? A comparison of allostatic load and the epigenetic clock(s). *Psychoneuroendocrinology* 2019;104:64–73.
18 Gupta RP, Mukherjee M, Sheikh A, *et al*. Persistent variations in national asthma mortality, hospital admissions and prevalence by socioeconomic status and region in England. *Thorax* 2018;73:706–12.
19 Bahreinian S, Ball GDC, Vander Leek TK, *et al*. Allostatic load biomarkers and asthma in adolescents. *Am J Respir Crit Care Med* 2013;187:144–52.
20 Zein JG, Erzurum SC. Asthma is different in women. *Curr Allergy Asthma Rep* 2015;15:28.
21 Knies G. *Understanding Society – the UK household longitudinal study: waves 1–4, user manual*. Colchester, UK: Institute for Social and Economic Research, University of Essex, 2014.
22 University of Essex. Institute for social and economic research NSR, Kantar public. understanding Society: waves 1-8, 2009-2017 and Harmonised BHPS: waves 1-18, 1991-2009. UK data service 2018.
23 McFall S, Petersen J, Kaminska O, *et al*. *Understanding Society–The UK household longitudinal study: waves 2 and 3 nurse health assessment, 2010–2012 guide to nurse health assessment*. Colchester, UK: Institute for Social and Economic Research, University of Essex, 2013.
24 Beckie TM. A systematic review of allostatic load, health, and health disparities. *Biol Res Nurs* 2012;14:311–46.
25 British Medical Association, Royal Pharmaceutical Society of Great Britain. British national formulary: March 2009. *Pharmaceutical Pr* 2009.

26 Global Initiative for Asthma (GINA). Pocket guide for asthma management and prevention (for adults and children older than 5 years): GINA 2018.
27 Foster M. What are equivalence scales? [cited 2018 4th April], 2009. Available: http://www.oecd.org/eco/growth/OECD-Note-EquivalenceScales.pdf
28 StataCorp. *Stata statistical software: release 14*. College Station: TX: StataCorp LP, 2015.
29 Kerkhof M, Tran TN, Soriano JB, *et al*. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. *Thorax* 2018;73:116–24.
30 Robertson T, Beveridge G, Bromley C. Allostatic load as a predictor of all-cause and cause-specific mortality in the general population: evidence from the Scottish health survey. *PLoS One* 2017;12:e0183297.
31 Johnson SC, Cavallaro FL, Leon DA. A systematic review of allostatic load in relation to socioeconomic position: poor fidelity and major inconsistencies in biomarkers employed. *Soc Sci Med* 2017;192:66–73.
32 To T, Simatovic J, Zhu J, *et al*. Asthma deaths in a large provincial health system. A 10-year population-based study. *Ann Am Thorac Soc* 2014;11:1210–7.
33 Pbert L, Madison JM, Druker S, *et al*. Effect of mindfulness training on asthma quality of life and lung function: a randomised controlled trial. *Thorax* 2012;67:769–76.
34 Takemura M, Matsumoto H, Niimi A, *et al*. High sensitivity C-reactive protein in asthma. *Eur Respir J* 2006;27:908–12.
35 DeBoer MD, Phillips BR, Mauger DT, *et al*. Effects of endogenous sex hormones on lung function and symptom control in adolescents with asthma. *BMC Pulm Med* 2018;18:58.
36 Kasperska-Zajac A. Asthma and dehydroepiandrosterone (DHEA): facts and hypotheses. *Inflammation* 2010;33:320–4.
37 Rutkowski K, Sowa P, Rutkowska-Talipska J, *et al*. Dehydroepiandrosterone (DHEA): hypes and hopes. *Drugs* 2014;74:1195–207.
38 Foster JM, McDonald VM, Guo M, *et al*. "I have lost in every facet of my life": the hidden burden of severe asthma. *Eur Respir J* 2017;50:1700765.
39 Chen S, Golam S, Myers J, *et al*. Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA steps 4 or 5 treatment. *Curr Med Res Opin* 2018:1–14.
40 Maninger N, Wolkowitz OM, Reus VI, *et al*. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). *Front Neuroendocrinol* 2009;30:65–91.