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DOI
10.1016/j.healthplace.2018.05.003

Publication date
2018

Document Version
Accepted author manuscript

Published in
Health and Place

Citation (APA)
Prior, L., Manley, D., & Jones, K. (2018). Stressed out? An investigation of whether allostatic load mediates associations between neighbourhood deprivation and health. *Health and Place*, *52*, 25-33. https://doi.org/10.1016/j.healthplace.2018.05.003

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Stressed out? An investigation of whether allostatic load mediates associations between neighbourhood deprivation and health

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Acknowledgements:

Understanding Society is an initiative funded by the Economic and Social Research Council and various Government Departments, with scientific leadership by the Institute for Social and Economic Research, University of Essex, and survey delivery by NatCen Social Research and Kantar Public. The research data are distributed by the UK Data Service. Lucy Prior is funded by an ESRC PhD studentship in Advanced Quantitative Methods (grant number ES/J50015X/1). Whilst working on this paper, some of David Manley's time was funded by the European Research Council under the European Union's Seventh Framework Programme (FP/2007-2013) /ERC Grant Agreement no. 615159 (ERC Consolidator Grant DEPRIVEDHOODS, Socio-spatial Inequality, Deprived Neighborhoods, and Neighborhood Effects). This article is the work of the authors, and the ESRC, ERC and the University of Bristol had no role in the design or writing of this article.

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Abstract

Deprived neighbourhoods have long been associated with poorer health outcomes. However, many quantitative studies have not evidenced the mechanisms through which place 'gets under the skin' to influence health. The increasing prevalence of biosocial data provides new opportunities to explore these mechanisms and incorporate them into models of contextual effects. The stress pathway is a key biosocial mechanism; however, few studies have explicitly tested it in neighbourhood associations. This paper addresses this gap by investigating whether allostatic load, a biological response to chronic stress, mediates relationships of neighbourhood deprivation to physical and mental health. Data from UK Understanding Society is used to undertaken a multilevel mediation analysis. Allostatic load is found to mediate the association between neighbourhood deprivation and health, substantiating the biological mechanism of the stress pathway. More deprived areas are associated with higher allostatic load, and in turn worse allostatic load relates to poorer physical and mental health. Allostatic load is a stronger mediator of physical health than mental health, suggesting the stress pathway is more pertinent to explaining physical health gradients. Heterogeneity in the results between physical and mental health suggests more research is needed to disentangle the biosocial processes that could be important to health and place relationships.

Key words: allostatic load, deprivation, health, neighbourhood, biosocial

1 Introduction

There is a long history of research seeking to better understand how where you live interacts with your health and wellbeing (Brown et al., 2010; Jones and Moon, 1992). Persistent health inequalities between areas mean local context (commonly referred to as 'the neighbourhood') remains a focal point of interest in health relationships (Office for National Statistics, 2014; World Health Organisation, 2008). It is widely acknowledged that living in disadvantaged areas negatively impacts your life chances. This idea underlies much of the neighbourhood effects research paradigm and has generally found support in the literature (Kawachi and Berkman, 2003; Van Ham et al., 2012). Given this consistency of findings, interest has turned towards investigating the mechanisms that may explain relationships between deprivation and health.

Within the literature which has unpacked the 'black-box' of neighbourhood effects (Macintyre et al., 2002), a developing area is concerned with biological plausibility. There is an extensive literature detailing how features of the social and physical environment may play a role in contextual relationships with health and wellbeing (see Diez Roux and Mair, 2010; Rosenberg, 2017). Now researchers are turning their attention to the question of how environments 'get under the skin'. The complexity of environment-health interactions, and their potential to accumulate over the lifecourse, makes research at the dynamic interface of the biological and social a fruitful avenue of inquiry. Considering biological plausibility in the embodiment of context can provide insight into pathways that are credible for a range of processes. Tracing the imprint of disadvantage also offers a powerful tool to comprehend histories of vulnerability, and thus to inform policy on health inequalities.

As yet, this literature has not been fully developed and further research is needed to understand processes of health and place relationships and to explore biosocial links in an explicit manner (see Authors, forthcoming). This paper contributes a test of the stress pathway model, which posits that

living in disadvantaged areas increases the stress burden residents are exposed to, raising the likelihood of poor health. To address some of the key gaps in the emergent biosocial literature, we adopt a multilevel perspective concerned with neighbourhood in combination with biodata and examine the role of a stress burden *within* relationships of place and health, using mediation analysis. We assess whether allostatic load, marking a cumulative biological weathering in response to chronic stress, mediates the association between neighbourhood deprivation and individual health.

2 Background

Previous studies have indicated the presence of associations between deprived neighbourhoods and health outcomes across a range of national contexts (Adams et al., 2009; Arcaya et al., 2016; Sundquist et al., 2004). Such studies have been instrumental in demonstrating the impact of neighbourhood on individual health and the inequalities of health status between areas (Wilson et al., 2010). However, many of these studies do not directly address the question of how the neighbourhood would impact the individual. Quasi-experimental studies, such as the Moving to Opportunity (MTO) and Gautreaux residential mobility programs in the US provide insight into neighbourhood and health relationships (Ludwig et al., 2012; Rosenbaum and Zuberi, 2010). For example, improvements in the mental health of those who moved to lower poverty neighbourhoods under MTO have been attributed to reductions in stress exposure (Katz et al., 2001). The role of perceptions and experiences of stress in deprivation-health relationships is a recurring theme in the neighbourhood literature and offers a pathway for exposing the mechanisms of neighbourhood effects.

The increased incorporation of biomarkers within large social surveys is facilitating analysis which appreciates the entanglement of biological and social phenomena. The stress pathway is one theorised biosocial model drawn upon to link places and health. It postulates that the fewer and poorer quality social and physical resources that characterise deprived areas shape exposure to

stressful experiences, as well as restricting opportunities for well-being. The resulting stress burden is proposed to negatively impact health (Daniel et al., 2008). The biological response to chronic stress can be captured using the concept of allostatic load, which represents a weathering on physiological functioning resulting from repeated and prolonged exposure to stressors (McEwen and Seeman, 1999; McEwen and Stellar, 1993). Whilst the acute stress response is adaptive in the short-term, chronic activation stimulates a cascade of dysregulations across multiple physiological systems. These dysregulations ultimately increase the chances of morbidity and mortality, contributing to allostatic load and the common language feeling of being 'stressed out' (Juster et al., 2010; McEwen, 2008).

To operationalise allostatic load, a set of biomarkers is typically used to construct a composite index, for instance, summarising the number of biomarkers falling into high risk quartiles (Seeman et al., 1997). Factor analysis has shown that biomarkers used to construct allostatic load measures tend to load onto a single common factor, suggesting this summary approach to be sufficient (Howard and Sparks, 2016; Wiley et al., 2016). Results by Wiley et al. (2016), comparing factor loadings of their full model with a series of models where different sub-systems and their associated biomarkers were dropped, were consistent with item parameter invariance. This implies the same latent factor representing allostatic load may be identified even if the underlying set of biomarkers varies (Wiley et al., 2016). Higher allostatic load has consistently been found to relate to mortality and worse health outcomes (Hwang et al., 2014; Juster et al., 2010). For example, allostatic load has been shown to be predictive of cognitive and physical functioning decline (Seeman et al., 1997), chronic diseases (Mattei et al., 2010) and depressive symptoms (Seplaki et al., 2006). Allostatic load, therefore, provides a valid tool to trace the biological memory of disadvantage over time and link neighbourhood circumstances to individual health.

Studies which have implicated stress exposure using allostatic load have focused on individual-level factors, such as socioeconomic status, poverty and adverse experiences (Barboza Solís et al., 2015;

Gruenewald et al., 2012; Kakinami et al., 2013). Others have invoked neighbourhood by examining how individual perceptions of neighbourhood features relate to allostatic load (Van Deurzen et al., 2016). By focusing on individual-level perspectives, researchers are missing the context of health relationships and are not recognising the inherently social construction of life (Krieger, 1994). Where place or neighbourhood characteristics have been explored, allostatic load has been positioned as an outcome rather than as an intervening variable in environment-health pathways. These studies have generally corroborated the negative health consequences of adverse neighbourhood circumstances on allostatic load (Bird et al., 2010; Brody et al., 2014; Theall et al., 2012). However, there remains a need for more studies examining the neighbourhood space, allostatic load and health in other national contexts; research using data from US studies has dominated the literature so far. This paper considers how allostatic load acts in pathways from neighbourhood circumstance to general states of health and functioning, for a nationally representative sample of Great Britain.

The potential of mediation analysis in helping to disentangle the mechanisms linking gradients in circumstance to health inequalities has been recognised. For example, Schulz et al. (2012) used the causal steps criteria (Baron and Kenny, 1986) to show the relationship of neighbourhood poverty to allostatic load was mediated by psychosocial stress for residents of Detroit. However, there have been very few studies to date which assess allostatic load as a mediator of health relationships. For instance, Hu et al. (2007) were not able to support allostatic load as a mediator of the relationship of socioeconomic status to self-rated health and activity limitations. In contrast, Sabbah et al. (2008) provided evidence of a mediating influence of allostatic load on socioeconomic gradients in periodontal and ischaemic heart disease. However, both studies relied on the attenuation of a previous relationship to evaluate the presence of mediation, an approach which is problematic as it does not allow researchers to distinguish a mediator from a confounder. This technique also does not follow recommendations for conducting mediation analysis which require that the indirect effect - that is the effect that travels through the mediator - must be investigated (Hayes, 2009). Moreover,

investigations that explicitly explore the role of allostatic load, and which do so in multilevel frameworks are currently lacking.

This paper aims to address these limitations by employing large-scale data from Great Britain to investigate the stress pathway, placing allostatic load as a mediator in the proposed causal pathway from neighbourhood deprivation to health. Figure 1 demonstrates the model of the stress pathway conceptualised in this study. As part of this assessment we hypothesise: (1) higher deprivation predicts worse allostatic load; (2) higher allostatic load is associated with worse physical and mental health; (3) higher deprivation relates to worse physical and mental health. To the author's knowledge this will offer a novel test of whether and how allostatic load acts as a mediator in a multilevel, neighbourhood framework.

<Figure 1 around here>

3 Methods

This study uses data from Understanding Society (Knies, 2016; University of Essex, 2016a). At Waves 2 and 3 (collected between 2010-2012) separate nurse health assessments were carried out and blood samples collected (University of Essex, 2014). The Wave 2 nurse assessment was undertaken on a subset of the General Population Sample component, with 10,175 persons consenting to have a blood sample taken. At Wave 3 the health survey was assessed on a subset of the former British Household Panel Survey sample: a smaller sample of 3,342 adults had a blood sample taken. Documentation of the nurse assessment and the biomarker data is available in McFall et al. (2014) and Benzeval et al. (2014). This paper combines the two biomarker samples, treating them as a single cross-sectional sample for the purpose of this analysis. Respondents from Northern Ireland were not included in the nurse health assessments; therefore, our sample is representative of Great Britain only.

Individual-level data was linked to neighbourhood context in the form of Lower Layer Super Output Areas (LSOAs and the equivalent Scottish Data Zones, DZs) using the 2011 Census boundaries (University of Essex, 2016b). The conceptualisation of neighbourhoods is a contested issue (Galster, 2001) and although employing this statistical unit may not be an ideal representation of an individual's context, employing statistical or administrative geographies is common practice in the neighbourhood literature. We elected to keep the neighbourhood unit similar to that adopted most commonly in the literature to aid comparisons as we are exploring an innovative means of understanding how neighbourhood context transmits to individuals. LSOAs and DZs are small geographical units, with around 1,600 and 800 individuals on average for LSOAs and DZs respectively (Flowerdew et al., 2007; Office for National Statistics, 2016). This offers a reasonable approximation to colloquial understandings of 'neighbourhood'. All models had 11387 individuals nested within 6629 neighbourhoods.

Health Outcomes

We report on two outcome variables, the 12-Item Short Form Health Survey (SF-12) physical and mental health component scores. The SF-12 physical health score covers physical functioning, limitations due to physical health, bodily pain, and general health. The mental health score addresses vitality, social functioning, limitations due to emotional problems, and mental health. Valid answers to source questions covering these features are converted to the SF-12 physical and mental health functioning scores, which are continuous scales running between 0 and 100, where higher scores are representative of better health (Ware et al., 2002). The SF-12 was developed as a measure of generic health status, and is a shorter alternative to the SF-36 health measure (Ware et al., 1995).

Neighbourhood Deprivation

Neighbourhood deprivation is measured using the Index of Multiple Deprivation (IMD, see Noble et al., (2006) for detail). The IMD serves to identify areas of concentrated deprivation at the small-area (LSOA) level. Whilst it would be ideal to measure deprivation at a consistent point in time, the devolved administrations within the UK run separate programs and as a result, data come from the 2015 English IMD (GOV.UK, 2015), the 2016 Scottish IMD (Scottish Government, 2016) and the 2014 Welsh IMD (StatsWales, 2015). The majority of indicators for the three measures are sourced from 2011 to 2015 (National Statistics for Scotland, 2016; Smith et al., 2015; Statistics for Wales, 2014). Each country's IMD is compiled in similar ways, producing a relative ranking of deprivation of small areas. However, the exact data sources and module content varies between countries so that each measure better reflects the national context. Therefore, quintiles of deprivation were calculated separately within each country. Here it is assumed that the relative nature of deprivation is captured similarly by the three national measures. Country of origin is additionally included in the models to account for differences between the English, Scottish and Welsh measures. The highest rates of deprivation are indicted by quintile 5.

Allostatic Load

Allostatic load represents a physiological 'wear-and-tear', characterised by dysregulation across multiple systems of body as a consequence of chronic exposure to stressful experiences (McEwen and Seeman, 1999). To represent allostatic load, this study uses 13 biomarkers from the cardiovascular, inflammatory, lipid and glucose metabolism systems, and the hypothalamic-pituitary (HPA) axis. Summaries are presented in Table 1. The biomarkers represent a similar suite to those used by previous studies with each marker utilised regularly in analyses (Schulz et al., 2012; Seeman et al., 1997; Wiley et al., 2016). Information on the analysis and measurement procedure for each biomarker can be found in the Biomarker User Guide (see Benzeval et al. (2014)).

<Table 1 around here>

A system risk score of allostatic load was created by calculating the proportion of biomarkers within each of the subsystems that fell into high-risk quartiles (this was the top quartile for every biomarker except for HDL cholesterol, albumin and DHEAs where the lowest quartile represents those most at risk), before combining the proportions across the systems to create a continuous score ranging from 0 to 5, where higher scores represent worse outcomes. This method accounts for the unequal number of biomarkers representing the different systems (Read and Grundy, 2014; Seeman et al., 2014). Measures were calculated for every participant, except where an individual lacked data on all biomarkers: where individuals were missing data on a biomarker this was treated as 'not at risk' in a maximum bias approach (Barboza Solís et al., 2015). Results were not significantly different using measures created only with those participants with non-missing information across all biomarkers. We also explored two additional constructions of allostatic load: a simple risk score and a total allostatic load score. The simple risk score was a count of the number of biomarkers for which participants fell into high-risk quartiles. The total allostatic load score was created by standardising each of the biomarkers into a z-score and taking the average of these z-scores. Sensitivity analyses (results available from the authors) showed findings were comparable across the three allostatic measures so only results for the system risk score are presented

Individual Socio-demographics

To control for the action of individual characteristics that may confound the neighbourhood deprivation effect and act as predictors of health status, the individual covariates of age, sex, ethnicity, employment status, marital status, education, welfare status and housing tenure were included in this analysis. Binary variables included sex, ethnicity, marital status and welfare status. Ethnicity was a comparison of non-white to white. Marital status compared those who were single, divorced, separated or widowed with those married, in a civil partnership or living as a couple.

Welfare status was calculated by combining the main means-tested benefits relating to disadvantaged status (Unemployment and National Insurance benefits, Income support, and Housing and Council Tax benefits), and recoding to receiving any of these benefits or none. Employment status was recoded to three categories: employed, retired, and inactive (comprised of unemployed, long term sick or disabled, those caring for family or home, full time students and other non-employed statuses). Education was captured through the highest educational qualification. Housing tenure was a categorical variable comprising: owned, socially rented, privately or other rented. See Table 2 for summaries of the variables.

<Table 2 around here>

Analysis

To unpack the black-box of neighbourhood effects we adopt a mediation approach. Mediation is conceived as a causal phenomenon, whereby the relationship between two variables is accounted for by a variable that is conceptually on the causal pathway between the exposure and the outcome – a mediator (Baron and Kenny, 1986). Here a multilevel analysis is used to investigate whether allostatic load mediates the association of neighbourhood deprivation with physical and mental health. A multilevel framework is required to simultaneously estimate at different levels of analysis and account for the clustering of individuals within neighbourhood units (Duncan et al., 1998; Jones and Duncan, 1995). Assessing the hypothesised model in Figure 1 requires fitting two multilevel equations for each health outcome, *i* and *j* subscripts indicate individual-level and neighbourhood-level respectively.

$$M_{ij} = \beta_1 0 + aX_j + \mu_{Mj} + e_{Mij} \quad (1)$$

$$Y_{ij} = \beta_2 0 + cX_j + bM_{ij} + b_1 MX_{ij} + \mu_{Yj} + e_{Yij} \quad (2)$$

Equation (1) predicts the mediator (M) by neighbourhood deprivation (X), assessing pathway *a* in Figure 1 and the first hypothesis. The second equation fits a two-level model predicting the health

outcome of interest (Y) by neighbourhood deprivation (X) and allostatic load (M). This second equation assesses whether hypotheses (2) and (3) are supported; it provides information on pathways *b* and *c* in Figure 1. An interaction between neighbourhood deprivation and allostatic load is additionally included in the second equation. Insights from the causal inference literature have emphasised the importance of accounting for potential interactions between the exposure and the mediator to making correct mediation inferences (Valeri and VanderWeele, 2013).

The effect of deprivation that travels through allostatic load, the indirect effect (*IE*), is calculated as the product of the effect of X on M in equation (1) and M on Y from equation (2), as in equation (3).

$$IE = a(b + b_1 X) \qquad (3)$$

If no interaction is present (if b_1 was zero), the equation for the indirect effect reduces to the simple *ab* product. The product method was chosen as an intuitive measure of the indirect effect, and one which facilitates explicit examination of the pathways of interest (Krull and MacKinnon, 2001; VanderWeele, 2016). Additionally, the difference method for identifying indirect effects, comparing the effect of the exposure before and after controlling for the mediator, has been criticised in the presence of exposure-mediator interactions (Kaufman et al., 2004).

As our measure of neighbourhood deprivation is categorical (with dummy variables included for quintiles 2 to 5 in the models) we identify four indirect effects, which we term *relative indirect effects* following the convention introduced by Hayes and Preacher (2014). Estimates of each of these indirect effects and their 95% confidence intervals were obtained from an iterated bias-corrected bootstrapping procedure creating 5000 resampled estimates, for 10 replicate sets to achieve convergence (see the MLwiN user's guide (Rasbash et al., 2017) for details of the bootstrapping process). Bias-corrected bootstrapping is considered an appropriate method to evaluate the indirect effect of a mediation analysis (MacKinnon et al., 2004; Pituch et al., 2006). The mean value of the *IE* calculated from the final iteration sets of 5000 is taken as the coefficient estimate of the relative indirect effects, and the 95% confidence intervals are obtained by finding

the values of the 2.5th and 97.5th percentiles of the estimated *IE* distributions. Bootstrapped estimates of the relative total effects, the sum effects of neighbourhood deprivation on health, are also reported as a comparison to the mediated effects.

Data preparation was conducted in Stata Version 14 (StataCorp, 2015), analysis was carried out in MLwiN version 3.01 (Charlton et al., 2017) using the runmlwin command (Leckie and Charlton, 2013) in Stata. All models were conducted with the final sample of 11387 participants who had full data across all variables.

4 Results

In a null model predicting allostatic load, the variance partitioning coefficient (VPC) indicated 14.8% of the variation lay between neighbourhoods. Significant higher-level variation remains in the fully adjusted model. The inclusion of neighbourhood deprivation and compositional characteristics reduced the variance at the neighbourhood-level to 7.8% in the final model.

Table 3 presents the results where the mediator, allostatic load, is the outcome: this is the assessment of pathway *a* on Figure 1. The first hypothesis is supported; areas characterised as more deprived are associated with higher, and therefore worsening, allostatic load scores[1]. This relationship is significant having controlled for socio-demographic characteristics. The results signal that neighbourhood deprivation acts most strongly through a heightened stress burden for those residing in areas in the most deprived circumstances. Figure 2 highlights the marked difference in predicted allostatic load score for someone resident in Q5 of neighbourhood deprivation, representing the most deprived areas, compared with Q4.

<Figure 2 around here>

[1] Results presented in Table 3 are for the system risk score. Results for the simple risk and total allostatic load scores were consistent in the direction and pattern of relationships identified, with differences in the size of effects and significance level due to the different metrics of the three allostatic measures.

Table 3 also presents results of models predicting the health outcomes, assessing pathways *b* and *c* in Figure 1, and the second and third hypotheses. In null models containing no covariates (not shown) the VPC showed 13.5% of the variation in physical health lay between neighbourhoods. For mental health, the VPC was slightly lower (11.9%). In the fully adjusted models, significant higher-level variation remains for both physical and mental health, with VPCs of 5.2% and 8.1% respectively. The larger proportion of variation explained by the inclusion of neighbourhood deprivation and individual characteristics suggests a stronger impact of deprivation on physical health than mental.

<Table 3 around here>

Allostatic load demonstrates a weaker association to mental health than to physical health. The expected decline in health status across the allostatic range is 11.92-points on the physical health scale, compared with 2.29-points on the mental health measure, holding other covariates at their average values[2]. This result could suggest a deficiency of the allostatic load measure employed to capture the biological dysregulations pertinent to mental health. Otherwise, given the reasonably high proportion of neighbourhood-level variation remaining in the final model for mental health (recall the VPC is 8.2%) there could be other processes at work not accounted for in this model, for instance psychosocial stress buffering through social capital and support. The associations of allostatic load to health are significant in all cases having controlled for individual-level confounders, however, and run in the theorised direction, supporting hypothesis (2).

Having adjusted for individual characteristics, higher levels of deprivation are associated with poorer mental and physical health (evidenced by increasingly negative coefficients), and so hypothesis (3) is supported. The association manifests primarily through an effect of residing in areas characterised as the most deprived (Q5) for both physical and mental health. The results also show that the

[2] Predictions obtained using the 'Customised Predictions' facility in MLwiN version 3.01, calculated for values from 0 to 5 on the allostatic load scale.

predicted health status of individuals living in Scotland or Wales is worse than for a person living in England, though this effect only appears significant for Wales.

An interaction was additionally identified between neighbourhood deprivation and allostatic load for physical health. As shown in Figure 3 the relationship of allostatic load with physical health is more pronounced for quintiles characterising neighbourhoods which are more deprived. For clarity 95% confidence intervals are not shown, if present they would show a significant difference between Q5 and the quintiles of lowest deprivation (Q1 and Q2). This interaction matches the theoretical background provided by the stress pathway: the negative health impact of a cumulative stress burden (allostatic load) is greater in more deprived areas. An interaction was tested for mental health but was not found to be significant or improve model fit so was, therefore, not included in the final models.

<Figure 3 around here>

Finding evidence for pathways linking deprivation to allostatic load, and allostatic load to physical and mental health supports a mediation pathway acting through a chronic stress burden. This result is substantiated by the relative indirect effects presented in Table 4. The majority of the relative indirect effects for both physical and mental health are significant; except for the indirect effect of being in Q2 compared to Q1, none of the confidence intervals include zero. The relative indirect effects are strongest for those in the most deprived areas (Q5) compared to the reference group. This gradient in the strength of the mediation is in line with the theoretical background of the stress pathway. Those residing in more deprived areas would be expected to experience increased exposure to stressful experiences, for instance from higher prevalence of crime or lack of social amenities, heightening the burden on their health (Ross and Mirowsky, 2001).

<Table 4 around here>

The relative indirect effects on mental health follow the same pattern as that for physical health. However, the strength of the mediation is weaker for mental health than physical health. Partially

standardised indirect effects are presented (IE_{ps}), these provide a measure of mediation effect size by giving the ratio of the indirect effect to the standard deviation of the response (Hayes, 2018; Miočević et al., 2018). This measure shows the insubstantial nature of the mediation effect for mental health; the largest expected decline in health status from living in the most deprived neighbourhoods is 0.009 of a standard deviation on the mental health score. For physical health in comparison, the predicted effect that travels indirectly through allostatic load of residing in areas characterised as the most deprived compared to the least deprived, is a decrease of 0.048 standard deviations in health score. The indirect effects for mental health are also relatively smaller in comparison to their total effects than for physical health.

5 Discussion

This paper is concerned with unpacking the black-box of neighbourhood effects through a biosocial lens. Often the literature reporting neighbourhood effects presents analysis in which the link between context and outcome is implicitly explored rather than explicitly tested. By investigating a proposed stress pathway acting between neighbourhoods and health we have moved forward to connect context and outcome directly in a biologically plausible manner. This was achieved by exploring whether allostatic load mediated the relationship between neighbourhood deprivation and both physical and mental health. The results support the three hypothesised pathways and our analysis of the relative indirect effects provides evidence to demonstrate allostatic load acts as a mediator within the deprivation-health relationship in Great Britain. Overall, our results support the stress pathway theorisation, and substantiate the potential role of allostatic load in health relationships illustrated by previous studies.

This study adds to the growing body of literature which cites the neighbourhood space and brings forward a concern for biological plausibility. We provide evidence for contextual associations of neighbourhood circumstances in Great Britain on allostatic load, corroborating the hypothesised stress pathway and the biological embedding of place in health. Health patterns routinely reflect

gradients of status and resources, and this extends to contextual conditions (Marmot, 2010; Theall et al., 2012). We found a gradient in the association of neighbourhood deprivation to allostatic load and our health outcomes; the strongest associations were consistently shown for the most deprived areas. The gradient in effects indicates the suitability of biosocial pathways to the investigation of health inequalities. It is possible to trace the imprint of varying exposures in the health states of different groups, by interrogating how the conditions of place are embodied through accumulated 'weathering' processes (Geronimus, 1992; McEwen and Stellar, 1993),

More generally, we have also highlighted the potential of mediation frameworks as a relevant technique to explore the complex pathways between neighbourhood conditions and health. By directly interrogating the indirect effect, this study improves on previous attempts to assess the potential of allostatic load to explain health gradients (Hu et al., 2007; Sabbah et al., 2008). This study thus expands the biosocial literature by assessing the action of allostatic load *within* the stress pathway, in a multilevel mediation study design. Allostatic load did significantly mediate the relationship of neighbourhood deprivation with physical and mental health, but with stronger support for the pathway to physical health. The mediating influence of allostatic load was strongest for areas characterised as the most deprived. Indeed, for physical health an interaction was present whereby the detrimental impact of allostatic load was heightened in more deprived compared with less deprived neighbourhoods.

There are limitations to the mediation method employed in this paper. The restriction to a cross-sectional design placed on the analysis by the biomarker sample prevents establishment of temporal ordering. Therefore, we cannot rule out reverse causation. Additionally, insights from the causal inference literature have stressed the importance of controlling for mediator-outcome confounders; the assumption of no confounding of this nature is required in order to make causal interpretations of indirect and direct effects (Pearl, 2001; Robins and Greenland, 1992; VanderWeele, 2016). By including key socio-demographic characteristics we control for some potential mediator-outcome

confounders, that is features which would affect both allostatic load and health status. For instance, those with higher allostatic load and those with poorer health are both more likely to be in worse social positions, for instance receiving welfare benefits or having fewer qualifications. However, there may be other unmeasured factors that act to confound the mediator-outcome relationship and so there remains the possibility for bias in the interpretation of the results.

The indirect effects for both health outcomes were statistically significant, however, the indirect effects for mental health were on the margin of insignificance and not substantial in size. Results by Seplaki et al. (2006) suggest the association of allostatic load to different health outcomes can vary by the type of allostatic load, in terms of the distribution of sets of biomarkers in high or low risk categories. It may be that by not differentiating between forms of allostatic load in the present study we are missing out on some of the relationship with mental health. Our sensitivity analyses using simple risk and total indices of allostatic load did demonstrate similarity in the pattern of results between measures, which gives confidence in the results found here. However, Howard and Sparks (2016) indicated the specific biological pathways through which allostatic load arises may vary by individual characteristics. Their study highlighted differences in the relative importance of the metabolic, inflammatory and cardiovascular subsystems by race/ethnicity and education. Future research would benefit from exploring different formulations of allostatic load that may account for the heterogeneity of pathways. Structural equation modelling would be a useful tool in this task, as it allows allostatic load to be formulated as a latent factor which could then be simultaneously evaluated for its role in pathways of interest.

The heterogeneity we identified between the physical and mental health outcomes may also reflect that the action of the stress pathway as we have operationalised it is more relevant to physical health than mental health. Other contextual characteristics, for instance segregation and neighbourhood stigma, alongside individual factors, particularly personality traits and psychosocial pathways that account for the perception of different situations, may be more germane to mental

health. Future research would benefit from deeper analysis of more complex mediating and interacting pathways. Researchers should bring factors that have previously been identified as important in the health and place literature, for instance disorder, social cohesion, and the role of green space, into a biosocial framework. Building on recent work such as a study by Robinette et al. (2018) which demonstrated higher perceived cohesion in the local area was related to lower cardiometabolic risk for older adults in the US, additionally implicating anxiety and physical activity in the pathway from cohesion to cardiometabolic risk.

Additionally, mental health is more transient in nature than physical health, incurring a higher degree of measurement error. This difficulty in capturing mental health may contribute to the diminished association we find in comparison to the physical health measure. The temporal variability of mental health may also mean that the impact of chronic stress exposure on mental health does not operate in the same cumulative fashion as for physical health and functioning. There is a clear need for longitudinal perspectives on biosocial pathways.

Longitudinal research is also needed to establish the order of causation and to take account of health-selective migration patterns which offer a competing hypothesis to the causal pathway proposed in this paper. For instance, Jiménez et al. (2015) did not evidence a relationship between baseline neighbourhood socioeconomic status and allostatic load at two years follow-up in a sample of older Puerto Ricans. The use of a longitudinal design in this study would have ruled out reverse causation due to the migration of those in poorer health to lower status neighbourhoods. We are not able to do this in the current study due to the cross-sectional nature of the biomarker data. Single-point-in-time measures may also underestimate the total, accumulated contribution of area conditions (Murray et al., 2013).

Future research should interrogate the temporality of relationships between neighbourhood characteristics, allostatic load and health. A lifecourse perspective which appreciates the importance of timing and the embedding of personal experience in the wider social and economic climate would

be a fruitful avenue for inquiry. It would be beneficial to integrate the multilevel biosocial thinking advocated by this paper with methods and insights from the lifecourse epidemiological literature, which has interrogated different lifecourse models of health relationships. For instance, Ploubidis et al. (2014) employed structural equation modelling to quantify the direct and indirect pathways of critical period, chains of risk, accumulation of risk and social drift hypotheses for the influence of socioeconomic position on later-life biomarkers. Gustafsson et al. (2014) exemplified the benefit of integrating lifecourse epidemiology and neighbourhood frameworks with the concept of allostatic load, demonstrating an accumulating impact of neighbourhood disadvantage on allostatic load.

In conclusion, this paper has provided a demonstration of the stress pathway through an interrogation of whether allostatic load acts as a mediator of neighbourhood circumstances on health. The results indicate support for an indirect pathway acting through allostatic load for adults in Great Britain, with a stronger and more substantial association demonstrated for physical health. Consistent gradation in the strength of effects across increasing quintiles of neighbourhood deprivation additionally corroborates the action of an enhanced stress burden for those living in more disadvantaged circumstances. The salience of biosocial ideas to health and place research is clear, particularly the importance of considering pathways for the cumulative influence of disadvantage on health. More research is needed to expose further discourses of marginalisation and inequality, and to understand histories of poor health for vulnerable groups. In this study, a substantial degree of higher-level variation remained unexplained for mental health, and for physical health the partially standardised indirect effects showed the largest effect was relatively small in comparison to the overall variation in physical health, around one twentieth of a standard deviation. These results show that while the pathway through allostatic load may be important it is not the whole story. Integrating biosocial ideas with insights from the place and health literature may reveal other important pathways for the embodiment of context. Longitudinal and lifecourse research exploring direct and indirect pathways will also be vital to researchers interested in the nature of place and health relationships.

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System	*Biomarker*	N	Mean(SD)	High Risk Cut-off Values
Cardiovascular	*Systolic Blood Pressure*	10,891	126.54(16.60)	≥136.5 mmhg
	Diastolic Blood Pressure	10,891	73.12(10.77)	≥80 mmhg
	Pulse Rate	10,891	68.84(10.74)	≥75.5 bpm
Lipid Metabolism	*HDL cholesterol*	12,858	1.55(0.46)	<1.2 mmol/l
	Total: HDL cholesterol ratio	12,857	3.75(1.36)	≥4.42
	Triglycerides	12,880	1.79(1.21)	≥2.2 mmol/l
	BMI	12,844	27.95(5.56)	≥30.8 kg/m^2
	Waist Circumference	13,060	93.82(14.45)	≥103 cm
Glucose Metabolism	*HbA1c*	12,145	37.25(8.19)	≥39 mmol/molhb
Inflammatory	*C-Reactive Protein*	12,513	3.26(7.14)	≥3.2 mg/l
	Fibrinogen	12,819	2.79(0.61)	≥3.2 g/l
	Albumin	12,902	46.78(2.95)	<45 g/l
HPA-axis	*DHEAs*	12,855	4.60(3.24)	<2.2 mol/l

Table 1. Biomarker summaries and high-risk quartile cut-off values.

	N		
Physical Health	11540	Mean(SD)	49.65(11.00)
Mental Health	11540	Mean(SD)	50.30(9.45)
Neighbourhood Deprivation	13228	Q1*	22.20%
		Q2	22.03%
		Q3	21.75%
		Q4	17.89%
		Q5	16.12%
Country	13228	England*	83.97%
		Wales	7.26%
		Scotland	8.76%
System Risk Allostatic Load	13226	Mean(SD)	1.15(0.97)
Age	13228	Mean(SD)	51.97(17.20)
Sex	13228	Male*	44.64%
		Female	55.36%
Ethnicity	13150	White*	95.29%
		Non-White	4.71%
Marital Status	13228	Married*	68.30%
		Single	31.70%
Employment Status	13228	Employed*	54.85%
		Retired	28.80%
		Inactive/Other	16.35%
Education	13095	Degree*	34.68%
		A Level	19.11%
		GSCE	20.83%
		Other	11.06%
		None	14.32%
Welfare Status	13213	Not Receiving*	87.79%
		Receiving	12.21%
Tenure	13211	Owned*	76.50%
		Socially Rented	13.54%
		Privately Rented	9.95%

Notes: * indicates reference category.

Table 2. Descriptive summaries of outcomes and covariates.

		Physical Health			*Mental Health*			*Allostatic Load*		
		β	S.E.		β	S.E.		β	S.E.	
Cons		60.574	0.877	**	55.420	0.811	**	-0.472	0.074	**
Neighbourhood	*Q1 (ref)*									
Deprivation	Q2	-0.362	0.405		-0.463	0.263		0.044	0.024	
	Q3	-0.274	0.410		-0.567	0.267	*	0.103	0.024	**
	Q4	-0.705	0.440		-0.853	0.286	**	0.100	0.026	**
	Q5	-1.509	0.479	**	-1.495	0.314	**	0.192	0.029	**
Country	*England (ref)*									
	Wales	-0.869	0.355	*	-0.749	0.345	*	0.006	0.031	
	Scotland	-0.373	0.314		-0.062	0.303		0.053	0.028	
Allostatic Load (AL)		-1.834	0.208	**	-0.461	0.103	**	-	-	
Neighbourhood	*Q1*AL(ref)*									
Deprivation*Allostatic	Q2*AL	-0.428	0.283		-	-		-	-	
Load (AL)	Q3*AL	-0.732	0.278	**	-	-		-	-	
	Q4*AL	-0.869	0.297	**	-	-		-	-	
	Q5*AL	-0.935	0.304	**	-	-		-	-	
Level 2 Variance		4.607	1.091	**	6.496	1.026	**	0.052	0.009	**
Level 1 Variance		83.447	1.504	**	73.511	1.343	**	0.616	0.011	**

Notes: Models adjusted for age, age2, sex, ethnicity, marital status, employment status, education level, welfare and tenure. ** and * indicate significance at 99% and 95% confidence levels respectively.

Table 3. Model results predicting physical health, mental health, and allostatic load.

		Indirect Effects					
		IE	95% CI	IE_{ps}	95% CI	*TE*	95% CI
Physical	Q2	-0.100	(-0.210, 0.006)	-0.009	(-0.019, 0.001)	-0.900	(-1.443, -0.370)
Health	Q3	-0.264	(-0.402, -0.137)	-0.024	(-0.037, -0.012)	-1.298	(-1.858, -0.740)
	Q4	-0.273	(-0.420, -0.130)	-0.025	(-0.038, -0.012)	-1.873	(-2.482, -1.280)
	Q5	-0.528	(-0.713, -0.358)	-0.048	(-0.065, -0.033)	-3.010	(-3.665, -2.331)
Mental	Q2	-0.020	(-0.047, 0.001)	-0.002	(-0.005, 0.000)	-0.481	(-0.993, 0.020)
Health	Q3	-0.047	(-0.081, -0.021)	-0.005	(-0.009, -0.002)	-0.616	(-1.147, -0.087)
	Q4	-0.046	(-0.080, -0.019)	-0.005	(-0.009, -0.002)	-0.897	(-1.469, -0.338)
	Q5	-0.088	(-0.137, -0.045)	-0.009	(-0.017, -0.004)	-1.589	(-2.202, -0.946)

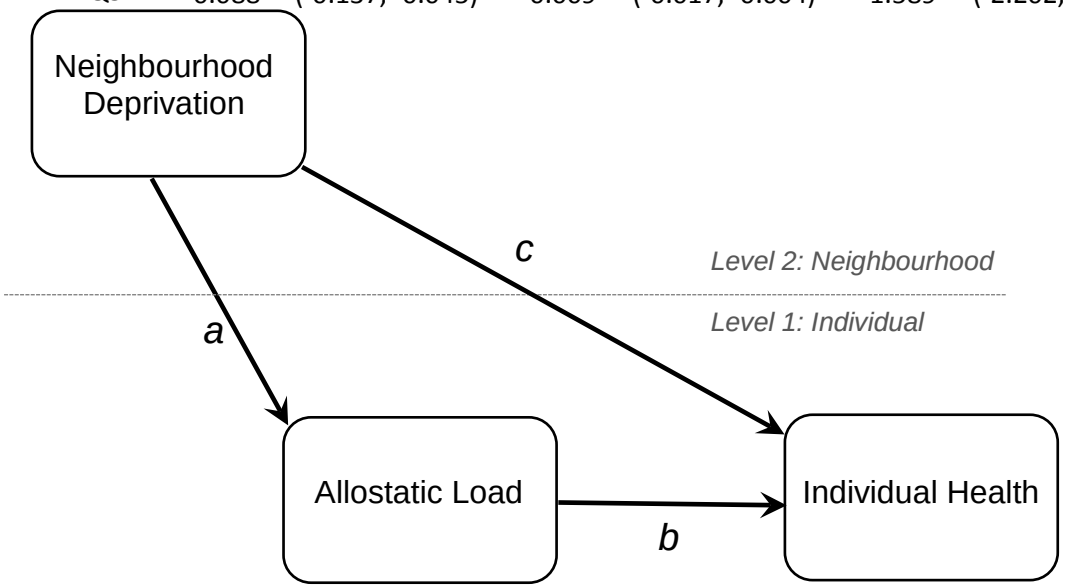
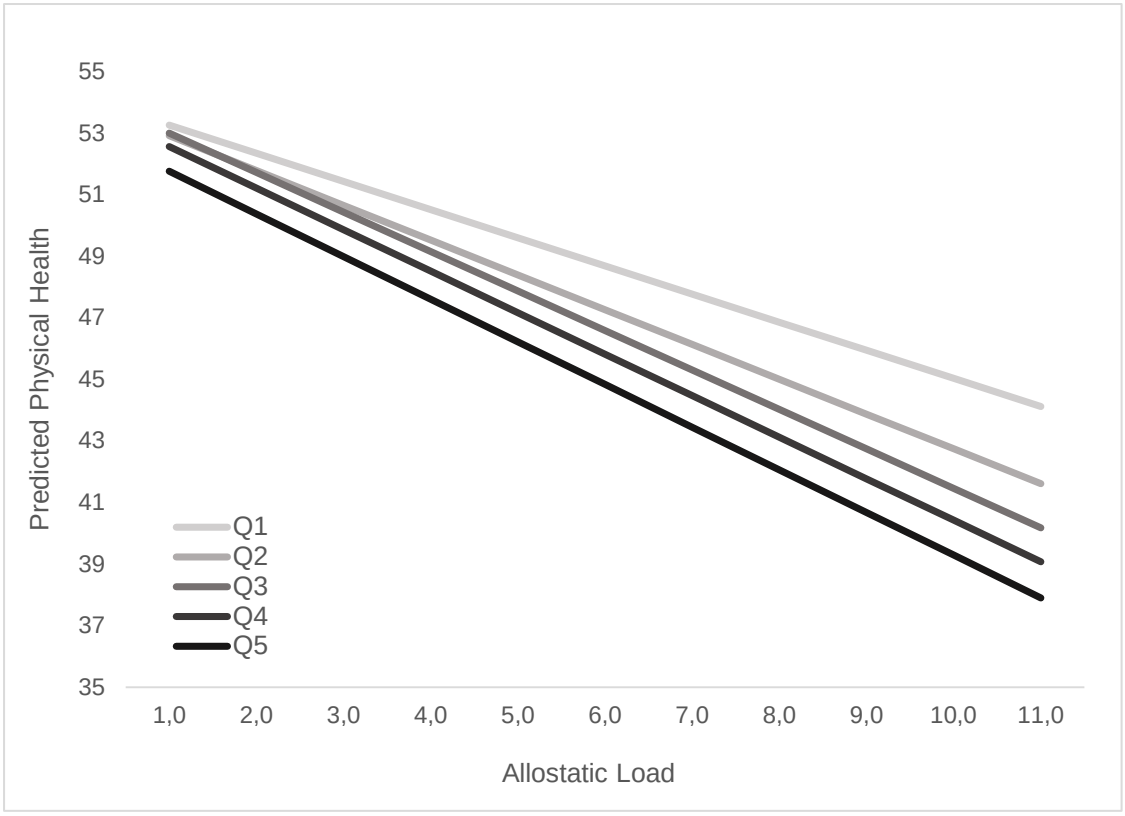


Table 4. Bootstrapped relative indirect effects (*IE)*, partially standardised indirect effects (IE_{ps}) and total effects (*TE*).

Figure 1. Diagram of the stress pathway.



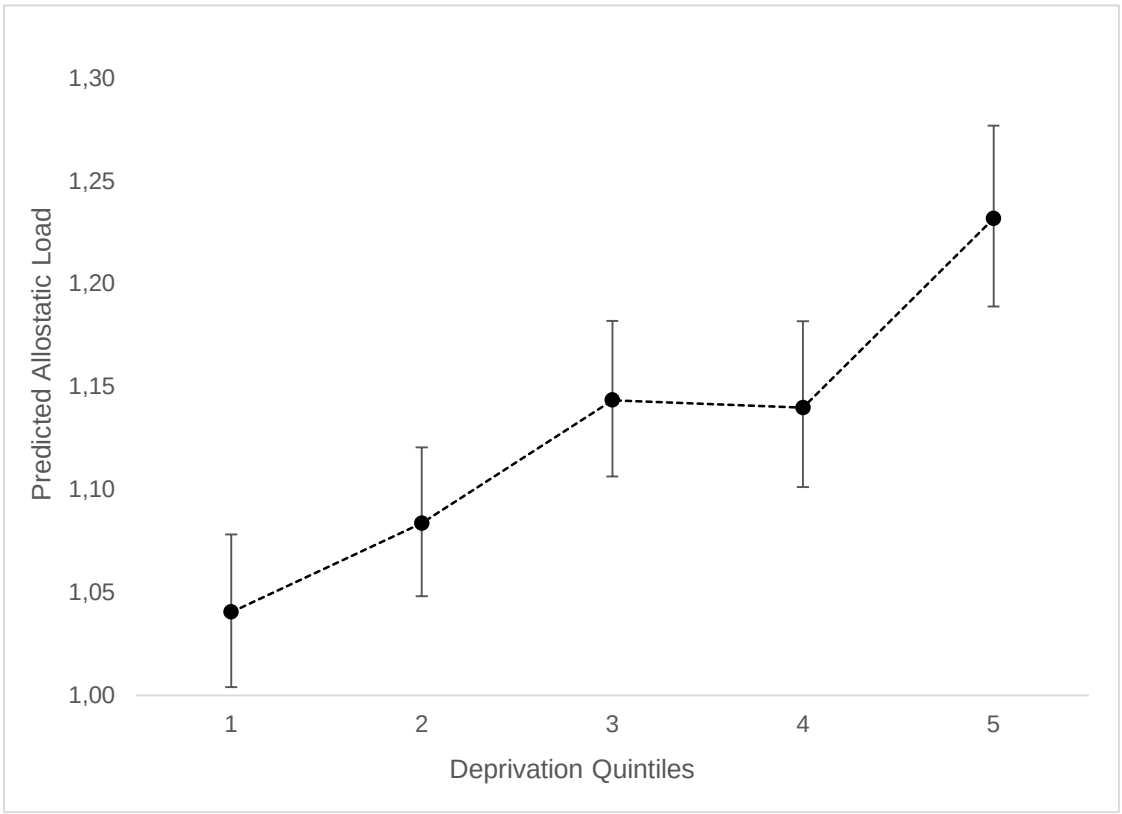


Figure 2. Mean predicted allostatic load score with 95% confidence intervals by quintiles of neighbourhood deprivation. Other covariates are held at their average values.

Figure 3. Mean predicted health scores by allostatic load and neighbourhood deprivation quintiles with other covariates held at their average values.