Socioeconomic Determinants of Inflammation and Neuroendocrine Activity: A Longitudinal Analysis of Compositional and Contextual Effects

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Abstract

Socioeconomic determinants are well-established modulators of inflammation and neuroendocrine activity. Less clear is whether neighbourhood-contextual or individual-compositional factors are more closely associated with gradients in these biomarkers. Here, we examine how immune and neuroendocrine activity are cross-sectionally and longitudinally nested in meso-level socioeconomic characteristics. Participants, male and female, aged ≥ 50, were recruited from the English Longitudinal Study of Ageing (ELSA). Neighbourhood (Index of Multiple Deprivation [IMD]) and individual (Wealth/Education/Occupational Social Class [OSC]) factors were drawn from wave 4 (baseline; 2008). Immune and neuroendocrine biomarkers (indexed by C-reactive protein [CRP; *n* = 3,968]; fibrinogen ([Fb] *n* = 3,932); white blood cell counts [WBCC; *n* = 4,022]; insulin-like growth factor-1 [IGF-1; *n* = 4,056]) were measured at baseline and 4-years later (wave 6; 2012). Covariates at baseline included demographic, clinical, and lifestyle variables. Lower socioeconomic status was associated with heighted inflammation and lower neuroendocrine activity unadjusted both cross-sectionally and longitudinally. With few exceptions, cross-sectional associations remained significant after full adjustment. Prospectively, low IMD remained associated with higher CRP and WBCC; wealth with WBCC; and education and OSC with Fb and WBCC. IMD-biomarker associations were reduced when wealth was simultaneously taken into account. Lifestyle accounted for the greatest variance in associations between socioeconomic indicators and inflammation (≤ 42.11%), but demographics were more salient to neuroendocrine activity (≤ 88.46%). Neighbourhood-contextual factors were stronger indicators of aberrant biomarker activity than individual-compositional factors in cross-sectional analyses but were largely explained by wealth differences prospectively. Therefore, immune and neuroendocrine changes depended on the composition of the population living in an area, rather than the area itself.

Introduction

Pro-inflammatory markers, such as C-reactive protein (CRP), fibrinogen (Fb), and leukocyte (white blood cell counts [WBCC]), and insulin-like growth factor-1 (IGF-1) an endocrine-mediated marker involved in anabolic processes, are of distinct yet interdependent importance in health and disease. Inflammation has downregulation effects on IGF-1 secretion,[1] while the IGF-1-axis has anti-inflammatory effects on inflammation.[2] Advances in molecular medicine and epidemiology have implicated inflammation as a principal biological pathway that underlies a host of health conditions and age-related physiological decline.[3–5] While IGF-1 promotes normal nerve and developmental growth, muscle mass and function, tissue survival, synaptic plasticity, and antiapoptotic-mediated signalling cascades, it also has a discrete role in human frailty, cognitive decline, and neuronal disorders.[6] The economic burden[7] and the gravity of these accumulative costs to health[8] have prompted a reconsideration of the mechanisms implicated in their aetiopathogenesis. Socioeconomic resource is one such factor.

Material deprivation can cause psychological stress, and is known to actuate a systemic level response through psychoneuroimmunological (PNI) and neuroendocrine pathways.[9–11] Among developed countries the UK has one of the largest gradients in deprivation,[12] with 7.8 million people in persistent poverty.[13] This is a concern for policy makers, not least, because of growing health disparities.[14] There is greater exposure to stress[15] and communicable disease in deprived areas, while individuals within those areas are, on average, more likely to engage in harmful health behaviours.[16] Still, they tend to have fewer educational, social, and psychological resources with which to cope,[15] with less availability of medical services and a reduced inclination to access care.[17] Elucidating the complex nature of poverty and the level of deprivation burden that is most impactful to biological processes is key to narrowing health disparities.[18]

An important distinction can be drawn between contextual and compositional socioeconomic indicators that are aggregated at the environmental and individual level respectively.[19] Contextual factors refer to characteristics of the place in which people live, and combine information from multiple domains, across education, employment, income, skills, training, housing, crime; health and disability,[20] in order to capture the multidimensional nature of deprivation and the poverty it signifies. In contrast, compositional factors relate to the idiosyncratic characteristics of the individuals within a neighbourhood. Extant literature supports that deprived populations are disproportionately exposed to environments characterised as pro-inflammatory.[21] Although compositional factors have been shown to predict facility in inflammatory and neuroendocrine states,[16] it is conceivable that contextual determinants are more proximal risk factors.[22] Such that health and disease are predominately shaped by social and spatial context.

Though socioeconomic indicators are well-established upstream determinants of systemic low-grade inflammation and neuroendocrine activity,[11,16,19] our interest is in the relative strength of contextual and compositional factors and prospective nature of these associations, as well as the extent to which different sets of covariates account for the gradient in outcomes. Differentiating between contextual and compositional effects is key to understanding how the environment confers risk on health after accounting for individual-level risk factors.[23] Ignoring this distinction increases the likelihood of an invalid transfer of results obtained at the ecological level to the individual level, as is the case when failing to account for ecology or context. Overlooking their dependent nature, along with the source of the dependency, can lead to significant findings where none exist.[24] Equally, understanding how inflammation and neuroendocrine processes are nested in compositional and contextual socioeconomic factors could bring some clarity to the structure of disadvantage,[14] and help to inform the focus, level, and magnitude of policies and interventions targeted at narrowing the health divide.

Older cohorts are an increasingly relevant demographic for two principal reasons. First, the pervasive role of social circumstances on the acceleration on core phenotypic, functional, molecular, and cellular aging processes.[25] Second, this phenomenon is further influenced by the confounding effects of inflammaging[26] and somatopause;[27] the gradual elevations of low-grade circulating inflammatory markers and decrements in the expression of IGF-1 circulating levels over time.

We assessed cross-sectional and longitudinal associations of neighbourhood-contextual and individual-compositional indicators on biomarker activity in a population-based sample of UK older adults, additionally examining the role of demographic, lifestyle, and clinical covariates in these associations. Given that cytokines are pleiotropic, misspecification of effects is possible when making isolated selections within a study,[28] so associations were tested using plasma

concentrations of CRP, Fb, and WBCC, in addition to serum IGF-1, a growth-related hormone that declines with age.[29] Neighbourhood-contextual indicators were expected to be stronger drivers of biomarker activity than individual-compositional indicators cross-sectionally and up to four-years later. As has been observed elsewhere,[30] factors associated with lifestyle were expected to account for greater variance in associations than demographic or clinical factors.

Method

Participants and procedures

Fully anonymised data were drawn from the English Longitudinal Study of Aging (ELSA), a multi-disciplinary prospective cohort study that began in 2002. The sample includes nationally representative men and women aged 50 years and older.[31] Data collection is performed in participants' homes, through computer-assisted personal interviews (CAPI) and self-completion questionnaires biennially, then nurse visits quadrennially for biological samples. Cross-sectional data and longitudinal exposures were taken from wave 4 (baseline; 2008) and longitudinal outcomes from wave 6 (follow-up; 2012). Using imputed data, 10,749 participants aged ≥50 had measures on exposures and covariates at baseline. The sample was reduced by death, study exit, declined consent or ineligibility (e.g., anticoagulant medication; haematological disorders; a history of convulsions). 5,841 participants had complete data on biomarkers at baseline and 3,562 also had complete data at follow-up. Each biomarker was analysed independently. After exclusions on CRP values >20mg/L (*n*=116), the analytic sample for CRP was 3,968 (36.92%), 3,932 (36.58%) for Fb, 4,022 (37.42%) for WBCC, and 4,056 (37.73%) for IGF-1. There were no significant differences between participants included and excluded from analyses. Participants provided written consent and ethical approval was granted by the National Research Ethics Service (London Multicentre Research Ethics Committee).

Exposures | Wave 4

Contextual (Neighbourhood-level) Socioeconomic Indicators

The 2004 index of multiple deprivation (i.e., neighbourhood deprivation) for England is a relative measure of deprivation that combines multiple area-level socioeconomic indicators into a single deprivation score. It is predicated on 38 indicators, across seven domains: education; employment; income; skills and training deprivation; barriers to housing and services; living environment deprivation and crime; health and disability. Neighbourhood deprivation was demarcated into tertiles; the first representing the most deprived on a gradient to the third that represents the least deprived (reference category).

Compositional (Individual-level) Socioeconomic Indicators

Wealth. Calculated by summating total household wealth, as determined by net wealth from property, possessions, housing, liquid assets; cash, savings, investments, artwork, and jewellery, net of debt, exclusive of pension wealth. Wealth was divided into tertiles; the first representing the least wealth and the third representing the greatest wealth (reference category).

Education. Categorised into higher education (i.e., degree or equivalent; reference category); primary/secondary/tertiary education (i.e., A-level, higher education below degree, GCSE or equivalent); and alternative/none (i.e., foreign or no qualifications).

Occupational Social Class. A three-category version of the National Statistics Socio-Economic Classification:[32] managerial and professional (reference category); intermediate; routine and manual.

Outcomes | Wave 6

Immune and Neuroendocrine Biomarkers

High-sensitivity plasma C-reactive protein (CRP; mg/L), plasma fibrinogen (Fb; g/L), leukocytes (white blood cell counts [WBCC]; 10^9/L), and serum insulin-like growth factor-1 (IGF-1; mmol/L) were dispatched to the Royal Victoria Infirmary (Newcastle-upon-Tyne, UK) for processing and analysis. Blood samples deemed insufficient or unsuitable (e.g., haemolysed; received >5 days post-collection) were discarded. Exclusion criteria included coagulation, haematological disorders, being on anticoagulant medication or having a history of convulsions.

C-reactive Protein. High-sensitivity plasma CRP (mg/L) was assayed using the N Latex CRP mono Immunoassay on the Behring Nephelometer II analyser (Dade Behring, Milton Keynes, UK). Intra and inter-assay coefficients of variation were <2%. The lower detection limit of the assay was 0.2 mg/L. CRP values >20 mg/L were excluded from analyses (*n*=116), as these were taken to reflect acute inflammatory processes rather than chronic inflammation.[30] CRP was treated as continuous, with higher values indicating greater levels of inflammation.

Fibrinogen. Plasma Fb (g/L) was analysed using a modification of the Clauss thrombin clotting method on the Organon Teknika MDA 180 coagulation analyser (Organon Teknika, Durham, USA). Intra and inter-assay coefficients of variation were <7%. The lower detection limit of the assay was 0.5 g/L. Fb was treated as continuous, with higher values indicating greater levels of inflammation.

Leukocytes (White Blood Cell Counts). WBCC was analysed as continuous counts per 10^9/L; measured on a haematology-automated analyser (Abbott Diagnostics Cell-Dyn 4000 and Sysmex XE), with higher values indicating greater levels of inflammation.

Insulin-like Growth Factor-1. Serum IGF-1 (nmol/L) was measured using the DPC Immulite 2000 method, by an electrochemiluminescent immunoassay on IDS ISYS Analyser. Inter and intra-assay coefficients of variation were <14%. IGF-1 was treated as continuous, with lower values indicating greater neuroendocrine activity.

Covariates

Factors likely to confound analyses were selected *a priori*, including *demographic variables*: age (≥50 years); sex (male; female); *clinical variables*: body mass index (BMI; calculated as weight in kilograms divided by height in meters squared [underweight:≤18.5; normal:18.6-24.9; overweight:25-29.9; obese:≥30kg/m2]); limiting longstanding illness (binary:- any long-term illness, disability, or infirmity that limits activity); and mobility difficulties (binary:- one or more difficulties mobilising [walking 100 yards; sitting 2-hours; rising from chairs after sitting long periods; climbing stairs; stooping, kneeling, crouching; reaching or extending arms above shoulders; pulling or pushing large objects; lifting or carrying objects over 10 pounds; picking-up a 5p coin]); *lifestyle variables*: smoking status (binary:- non-smokers/ex-smokers or smokers); alcohol consumption (binary:- low <3 or high ≥3 day weekly); physical activity (binary:- sedentary or moderate/vigorous weekly activity). Reference categories were being male, of normal weight, not having a limiting longstanding illness, being fully mobile, a non-smoker/ex-smoker, having low alcohol consumption, and being physically active.

Imputation. Missingness ranged from 0.00-52.33% (Supplementary [S] Table 4). Given the possibility of bias in complete case analyses,[33,34] missing values on exposures and covariates were imputed using missForest based on Random Forests, an iterative imputation method, in RStudio v.1.4.1717. In the presence of nonlinearity and interactions missForest outperformed prominent imputation methods, such as multivariate imputation by chained equations and *k*-nearest neighbours.[35] In ELSA, socioeconomic variables are the main drivers of attrition,[31] so the assumption that missingness was at random (MAR) was likely to be met. The imputation of the missing values yielded a minimal error for continuous variables (Normalized Root Mean Squared Error=0.02%) and categorical variables (proportion of falsely classified=0.20%). Imputed and observed data were homogenous (Table S4).

Statistical Analyses

Baseline characteristics were expressed as means and proportions. Logarithmic transformation was performed on CRP, WBCC, and IGF-1 values because of their originally skewed distribution. Fb was normally distributed. Cross-sectional analyses used multiple linear regressions to assess associations between exposures and outcomes at wave 4 (2008). Longitudinal analyses extended this to outcomes at wave 6 (2012). Results were presented as unstandardised (B) regression coefficients with standard errors (SE). Analyses were two-tailed. The basic model for the analysis can be expressed as: ($\hat{Y}_i = B_0 + B_1X_{1i} + B_2X_{2i} + ... + B_pX_{pi} + u_i$ where $\hat{Y}$ is the predicted value of the outcome; B_0 is the value of $\hat{Y}$ when all exposures equal zero; B_1 through B_p are the estimated regression coefficients, X_1-X_p are distinct covariates, and u is the error term). Each regression coefficient represents the change in $\hat{Y}$ relative to a one-unit change in the respective exposure. Independent multivariate models were fitted to understand the role of different sets of covariates on associations. Biomarkers were modelled independently as CRP was linearly correlated with Fb (r=0.310), WBCC (r=0.262), and IGF-1 (r=0.158) at p<0.001. No further issues existed with collinearity and all models met regression assumptions. The unadjusted model (1), that conditioned on the baseline biomarker being measured, was included in all models. Model 2 adjusted for age and sex (*demographic variables*). Model 3 adjusted for BMI, limiting longstanding illness, and mobility difficulties (*clinical variables*); Model 4 adjusted for smoking status, alcohol consumption, and physical activity (*lifestyle variables*); Model 5 adjusted for all covariates. To test the extent to which different models explained associations, the B for outcomes were calculated using the percentage of the protective association explained (PPAE); a well-established epidemiological method[36] using the formula: (where X is the model tested)PPAE = (B [crude model 1 and model X] – B [crude model 1] / (1-B [crude model 1]). Data analyses were conducted in Stata 17.1 (StataCorp, TX, USA).

Sensitivity Analyses

Four sensitivity analyses were carried out on longitudinal associations. First, sets of covariates were added sequentially rather than independently. Second, due to the potentially confounding effects of inflammaging and somatopause, the moderating effect of age was tested (dichotomised by mean age [≥64.25 years]). Third, the exclusion of CRP values thought to represent acute inflammatory processes (≥20 mg/L) was reassessed on the basis of arguments put

forward by Giollabhui et al. (2020)[37], so regressions were repeated including those values. Fourth, analyses used complete cases to compare the efficiency and coverage of confidence intervals for the estimated coefficients and to ensure results were not an artefact of the imputed data. Association analyses replicated that in imputed data. The analytical sample formation is illustrated in Figure S1.

Results

Descriptive statistics for the exposures and outcomes are shown in Table 1. The sample comprised 3,562 individuals for whom total baseline data was available. Of these, 44.67% were male, 55.33% female, aged on average 64.26 years (±8.35; $_{range}$50-99). Participants were, on average, overweight (72.38%), moderately to vigorously active (75.77%), with no limiting longstanding illness (72.18%), and were non-smokers (87.73%), who consumed alcohol less than three days in a given week (63.42%). But there was an equal balance of those with and without mobility difficulties. Biomarkers were stable on average from baseline to follow-up, although individual trajectories varied widely.

Cross-sectional associations between socioeconomic indicators and biomarkers

All associations between socioeconomic indicators and biomarker activity were significant in the unadjusted model (Table 2). Lower socioeconomic status was associated with higher concentrations of CRP, Fb, and WBCC, and with lower IGF-1 (p<0.001). The association between neighbourhood deprivation and IGF-1 remained significant in the fully adjusted model, but the relationships with inflammatory markers were no longer significant when covariates were taken into account. After full adjustment, associations between individual socioeconomic indicators and biomarkers were significant with two exceptions; education and IGF-1; OSC and WBCC.

Longitudinal associations between socioeconomic indicators and biomarkers

Across the 4-year follow-up period, all socioeconomic indicators were longitudinally associated with biomarker activity in basic models adjusted only for baseline biomarker levels (Table 3). Overall, lower socioeconomic status was associated with greater future inflammation and lower IGF-1 concentration. Some attenuation was seen after full adjustment, but neighbourhood deprivation remained associated with CRP and WBCC, as was wealth with WBCC, and education and occupation with Fb and WBCC. Other associations were lost after taking covariates into account.

Associations between neighbourhood indicators and biomarkers when accounting for individual-compositional indicators

After full adjustment, neighbourhood deprivation was longitudinally associated with higher CRP and WBCC over the four-year period (Table 4). These associations remained robust to the inclusion of education and occupation, but they were not longer significant after wealth and other covariates together were taken into account.

Percentage of protective association explained (PPAE) for models assessing socioeconomic indicators in biomarker activity

Covariates accounted for a varying degree of the association between socioeconomic indicators and biomarkers (Table 5). The three sets of covariates in combination, accounted for 11.76-92.31% of the PPAE. *Clinical variables* (BMI; limiting longstanding illness; mobility difficulties) explained between 9.09-35.29% of the variance. *Lifestyle variables* (smoking status; alcohol consumption; physical activity) accounted for the greatest PPAE in CRP, Fb, and WBCC (≤42.11%). But *demographic variables* (age; sex) were most salient to IGF-1 (≤88.46%).

Sensitivity Analyses

First, there was a consistent pattern of results when covariates were added sequentially rather than independently to the longitudinal analyses, suggesting that findings were not biased by model strategy (Table S1). Second, there were no significant interactions between socioeconomic indicators and age, suggesting that inflammaging and somatopause were not biasing results (Table S2). Third, results were materially unchanged when CRP values ≥20 mg/L were included in analyses, suggesting that associations were robust to the inclusion of these very high values (Table S3). Fourth, there was a substantial overlap in confidence intervals between the analyses performed in complete cases versus imputed data in the main analyses (Table S5).

Discussion

In this large longitudinal population study of UK older adults, neighbourhood contextual and individual compositional indicators of socioeconomic status were associated with heightened inflammation and low IGF-1 concentrations in models adjusted for baseline biomarkers, implying a higher risk to the overall systemic status of individuals with fewer socioeconomic resources. It is striking that these socioeconomic effects were observed over a 4-year period, and that many remained independent of a comprehensive selection of covariates. In particular, associations between all four socioeconomic indicators and greater WBCC remained significant after taking demographic, clinical, and lifestyle factors into account. Contrary to our hypothesis, neighbourhood contextual indicators were weaker drivers of inflammation and neuroendocrine activity than were individual compositional indicators. Certainly, in the case of WBCC,

neighbourhood effects survived individual differences in education and OSC, but significance was lost when wealth was taken into account. As expected, lifestyle factors accounted for a greater proportion of the variance in socioeconomic associations with inflammation than the other sets of covariates, but this was not so for concentrations of IGF-1 where demographics were more salient.

Interestingly, the variations in immune and neuroendocrine activity observed between our cross-sectional and longitudinal associations allude to possible socioeconomic differences in immune and neuroendocrine expression over time. While contexts and health can change over time,[24] consistent UK geographical patterns of deprivation have been reported over a century,[18,38] with more stability in the deprivation profile seen in geographically larger areas.[18]

There are reciprocal relationships between the complex physiological processes aimed at homeostatic balance, that could explain differences in effect sizes, and the temporal changes seen in the biological pattern of results within our data cross-sectionally and longitudinally.[39] Fb is involved in processes other than inflammation, such as haemostasis and angiogenesis. CRP, by contrast, has high sensitivity to insult, as the major human acute-phase protein, so the rapidity and magnitude of effects may be more substantial.[30] IGF-1 in circulation is downregulated by inflammatory cytokines[2], so cytokine expression may have attenuated the independent predictive value of socioeconomic determinants in IGF-1 at the cellular level. Interactions as crosstalk and antagonism are possible, since low IGF-1 also antagonises the CRP mechanism through the activation of a number of intracellular signalling pathways, which may have reduced CRP expression prospectively.[39]

The magnitude of associations between socioeconomic determinants and inflammation varies widely across individual studies;[16] attributable in part to variations in sample characteristics and study design, including principals used to limit confounding bias.[40] But, meta-analytic findings by Muscatell and colleagues (2020),[16] from 43 papers (n = 111,156), revealed that populations of lower socioeconomic status, defined by income, education, or occupation, experience higher levels of systemic inflammation, indexed by CRP and interlukin-6 (the chief stimulator of acute-phase protein production). Although less consistent for Fb and WBCC, this is echoed by our cross-sectional findings for CRP and IGF-1, with additional evidence provided on the upregulation of WBCC longitudinally in a sample of community dwelling older adults. In other words, deprivation can set individuals on an adverse immune-neuroendocrine trajectory that can even be observed among non-clinical populations. Extant literature has shown that CRP is higher among those with less wealth,[41,42] lower education,[43,44] and lower occupation.[43,45] While wealth,[42,46] education,[15,42,46,47] and occupation[15,43,46] have been shown to be correlates of change in circulating Fb, and lower education and occupation are known to be associated with elevated WBCC.[15,43] However, most studies are cross-sectional, so no inferences can be made on the causal direction of these results.

A substantial literature support that where you live, over and above individual characteristics, shape individual health and health inequalities among populations.[11,19,22,48] However, our results cast doubt on research that has implicated neighbourhood determinants in inflammation and neuroendocrine processes without consideration being given to individual effects in the study design. It may be that we have yet to elucidate the exact contextual mechanisms for environmental factors that appear to modulate inflammation and neuroendocrine activity.

As is documented elsewhere,[11] socioeconomic differences in inflammation and neuroendocrine activity were mostly explained by variations in lifestyle; smoking status, alcohol consumption and physical activity specifically. This confirms our hypotheses. The PPAE for each model has not been described in this context before. Lifestyle explained up to a half of the variance in associations between socioeconomic factors and inflammation. Remarkably, the PPAE for the demographics model accounted for over four fifths of the association between socioeconomic indicators and neuroendocrine activity. This was an unexpected result but may be explained by the sensitivity of IGF-1 to the somatopause.

There are a number of strengths of the present study. We used a large, well-characterised general population longitudinal cohort linked to census indicators of objectively measured contextual characteristics.[31] We provide information on pre-disease mechanisms that allow for a richer understanding of the deprivation-health gradient before disease become evident.[14] We also benefited from a comprehensive calculation of wealth that is unavailable in most studies; computed on the basis of precise information on multiple individual components rather than a broad categorisation of assets.[31] Although the multiple imputation strategy did not manage missing data on outcomes, results were consistent with complete case analyses.

However, results should be interpreted in light of some limitations. First, models based on nested counterfactuals rest on strong assumptions about confounding.[49] But, as with all observational studies, we cannot exclude the risk of unobserved confounding and residual confounding due to time varying intervals between the assessment of exposures and outcomes. Second, while ELSA is a demographically representative cohort, the majority of the sample are of White European origin, so findings may not be generalisable to other ethnic groups.[31] Residential areas within the UK are not monolithic, so although the index of multiple deprivation is calculated at a detailed level of areas, typically with 1,000–3,000 residents, most areas are heterogenous. Contextual indicators may therefore be underestimated for some and overestimated for others in the same area, leading to the ecological fallacy.[50]

Conclusion

We produced several key findings in the first known prospective population-based study to simultaneously examine the magnitude and prospective facility of socioeconomic determinants at the contextual and compositional level in immune and neuroendocrine activity, in addition to the role of covariates in these associations. This study has addressed the issue of whether socioeconomic variations in immune and neuroendocrine biomarkers are related to neighbourhood and individual-level factors independently of one another. We found that neighbourhood associations were primarily dependent on the composition of those living in the area, rather than the area itself. Examining disparities in immune and neuroendocrine status through the lens of compositional factors can improve the surveillance of important equity issues[23] and steer interventions toward individual-level prescriptions, over a broader society approach.

Declarations

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Tables

Tables 1-5 are in the supplementary files section.

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