Christopher J. Gidlow, Graham Smith, David Martinez, Richard Wilson, Paul Trinder, Regina Gražulevičienė, Mark J. Nieuwenhuijsen, **Research note: Natural environments and prescribing in England**, *Landscape and Urban Planning*, Available online 16 March 2016, ISSN 0169-2046, http://dx.doi.org/10.1016/j.landurbplan.2016.02.002

http://www.sciencedirect.com/science/article/pii/S016920461600008

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**Keywords**:

Nature, Mental health, Anti-depressants, Cardiovascular disease

## Highlights

- All-cause mortality was lower in areas with higher density of natural environment
- The association was strongest in the most deprived areas
- Cardiovascular prescribing was positively associated with natural environment
- Non-significant negative association for anti-depressant prescribing.

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**ABSTRACT**

Studies using routinely gathered data increasingly show associations between area-level green space and health. However, the environment exposure measures often include only urban green space and there has been limited use of prescribing data as a proxy health indicator. This brief report presents a small-area ecological study of associations between natural environment (including private gardens and water) and the volume and cost of prescribing for cardiovascular conditions and depression in England, with confirmatory analysis using all-cause mortality (in adults aged 15-65 years). Using Besag, York and Molliè (BYM) models to adjust for known confounders and unaccounted-for spatial autocorrelation, we found a statistically significant association of lower mortality in areas with higher area density of natural environment, which was strongest in more deprived areas. There was some evidence of a positive association between cardiovascular prescribing and area density of natural environment, with a non-significant trend towards lower anti-depressant prescribing in areas with higher natural environment density. Apparently beneficial relationships between all-cause mortality and natural environment were not observed for prescribing data, but we advocate further exploration focusing on prescribing for mental health and other conditions with plausible links.

## INTRODUCTION

There is broad consensus that exposure to nature is beneficial to human health (Hartig, Mitchell, de Vries, & Frumkin, 2014). Epidemiological studies using routinely gathered datasets have shown that area-level green space exposure is positively associated with mortality, morbidity and self-reported health (Maas, Verheij, Groenewegen, de Vries, & Spreeuwenberg, 2006; Mitchell & Popham, 2007), mental health (Gascon et al., 2015; White, Alcock, Wheeler, & Depledge, 2013), and health inequalities (Mitchell & Popham, 2008).

In the UK, there are many datasets and indicators that can be used to investigate the health-green space relationship (Park, O'Brien, Roe, Ward Thompson, & Mitchell, 2011). In most cases natural environmental exposure measures have been limited to urban green space and usually excluding private gardens, with some exceptions (White et al., 2013). Scope for detailed characterisation of the natural environment on a national scale is somewhat limited by the available data. But there is reason to explore more inclusive definitions of natural environments given the growing evidence for health benefits of passive contact with nature (e.g., having a view of nature from your home), gardening (Annerstedt & Währborg, 2011), and some evidence and growing interest in the link between exposure to natural water environments (or ‘blue space’) and health benefit (Völker & Kistemann, 2011; Wheeler, White, Stahl-Timmins, & Depledge, 2012).

With respect to health indicators, there has been little analysis of prescribing levels in relation to natural environments. In 2011, national prescribing data were made publically available at general practice level, reporting the amount and cost of prescriptions aggregated by British National Formulary (BNF) code. An early published analysis of medications for diabetes and attention deficit hyperactivity disorder were compared with disease incidence (Rowlingson, Lawson, Taylor, & Diggle, 2013). The authors concluded that data could be mapped for meaningful observation of geographical disparities in the level and associated cost of prescribing. Subsequently, Taylor et al. (2015) reported a significant, albeit weak association, linking a higher volume of street trees with fewer anti-depressant prescriptions across 33 boroughs of London. This, again, provided useful proof of concept evidence with a relatively specific natural environment measure, but was limited to a small number of data points. So further exploration of prescribing data in relation to natural environments is warranted.

The present study selected prescribing for two condition types, cardiovascular conditions and depression, to explore possible associations with natural environment at small area-level. These were selected given the biologically plausible associations of cardiovascular and mental health with natural environment, which have been shown in some previous studies (outlined above). Moreover, they provide examples of prevalent mental and physical health conditions with considerable associated health service costs. Our specific aims were to: (i) confirm the previously reported area-level green space-all-cause mortality association for England (Mitchell & Popham, 2008) using natural environment indicators that included private gardens and blue space; (ii) explore associations with volume and cost of prescribing for cardiovascular conditions and depression. This work was undertaken as part of the FP7-funded PHENOTYPE project (Nieuwenhuijsen et al., 2014). Ethical approval was granted by the University ethics committee.

## METHODS

### Green space exposure

Green space exposure was generated from the Generalised Land Use Database (GLUD) 2005 (DCLG, 2005). The GLUD reports the total area of land use in broad categories, including green space, woodland, farming and agricultural land, residential gardens and water bodies (blue space). These categories were used to generate the primary natural environment exposure indicator, *Green/Blue* (all natural land, including residential gardens and blue space), which was in keeping with the broad definition of natural environment within the PHENOTYPE project. Another exposure indicator, *Green* (including residential gardens, but not blue space), was used for sensitivity analysis to explore the contribution of blue space. Both were negatively correlated with all-cause mortality (*Green/Blue* $r=-.210$, $p<.001$; *Green* $r=-.209$, $p<.001$).

### Prescribing data

All data and associated analyses were performed at Lower Level Super Output Area (LSOA) level, where mean LSOA population size is approximately 1,600 people, and mean area size is approximately 88 hectares and 1819 hectares for urban and rural LSOAs, respectively. Data on the number of items (or volume) and cost of items prescribed for the 12 months of 2011 were downloaded from the Health and Social Care Information Centre (HSCIC) website (http://www.hscic.gov.uk/gpprescribingdata) for two British National Formulary categories: (i) Cardiovascular (2.1-2.13), such as medications for hypertension and heart failure, anti-anginal drugs, anticoagulants, antiplatelet drugs, and lipid-regulating drugs; (ii) antidepressants (4.3; http://www.bnf.org/bnf/index.htm). Actual Cost, not the Net Ingredient Cost data were used. Rather than reflecting just the basic price of a drug, Actual Cost includes dispensing costs, fees and discounts.

Data are available at general practice level. To allocate practice level data to LSOAs for analysis with natural environment data, a lookup table was created. It was derived from three years of Hospital Episode Statistics (HES) data, but excluded any LSOA from a practice if it contributed less than 2% of the total practice population. Re-distribution of prescribing data to LSOAs was tested using actual patient addresses that were available in one city (with 55 general practices) and showed good agreement (r=.897), suggesting appropriate allocation of data to LSOAs. LSOA population data for 2011 used revised boundaries from the 2011 Census whereas the HES lookup table used the previous version of LSOA boundaries from the 2001 Census. Only LSOAs that have remained the same, split or been merged were included, which provided a total of 32,250 LSOAs for analysis of prescribing data. The number (or volume) of prescriptions and associated costs per head of LSOA population were used.

**Mortality data**

We obtained anonymised, individual mortality records from the UK Office for National Statistics and extracted those aged 15 to 65 years, approximately equating to the adult working population. The records covered every death registered in England in 2011, with age at death and sex, and linked them to the LSOA of residence based on postcode. Data were used to generate Standardised Mortality Ratios (SMR, all-causes) for each LSOA.

**Confounder variables**

A number of other variables were used to adjust for other plausible influences on mortality and morbidity using a similar approach to others performing previous green space-mortality analysis (Mitchell & Popham, 2008).

*Deprivation*. Three sub-domains of the Index of Multiple Deprivation (IMD) used were: income deprivation; education, skills, and training; and living environment, which includes housing condition, lack of central heating, air quality and road traffic accidents (Communities and Local Government, 2010). For stratified analysis, income deprivation tertiles were used, where 1=least deprived and 3=most deprived tertile.

*Urbanicity*. A dichotomous urban/rural classification was used to classify LSOAs as urban (settlements with >10,000 residents) or rural (town and fringe; villages, hamlets and isolated dwellings) (Bibby & Brindley, 2013).

*Ethnicity*. The basic ethnicity indicator was the percentage of each LSOA population classified as White British in the 2011 Census (where high values indicate lower presence of other ethnic groups).

## Statistical Analyses

To aid interpretation, natural environment coverage was categorized as <25%, 25-49.9%, 50-74.9%, ≥75% (similar to Richardson & Mitchell (2010)). The relationship between LSOA-level natural environment coverage or density and the outcome variables for mortality and prescribing were explored using Besag, York and Molliè (BYM) models (Besag, York, & Mollié, 1991). These Poisson models included random effect terms for spatial and non-spatial heterogeneity that account for known confounders, while adjusting for unknown for spatial autocorrelation in the data. For age-sex standardised mortality (SMR), zero-inflated Poisson regression was used given the large number of zero counts. Separate models, unadjusted and adjusted, were run for SMR (as confirmation of the model), cardiovascular prescribing volume and cost, anti-depressant prescribing volume and cost. Adjusted models included: deprivation in education, skills, and training; deprivation in the living environment; urban-rural classification. For prescribing data, which could not be age-standardised, the proportions of the LSOA population in different age groups were included in models (20-64 yr, ≥65 yr). Adjusted models were run with *Green/Blue* as the exposure variable, and then repeated with *Green* (sensitivity analysis). Finally, we performed stratified analysis with the *Green/Blue* exposure variable by income tertile.

# RESULTS

## Mortality and natural environment

The proportion of land per LSOA accounted for by different types of natural environment were: green space 42.2±29.8%; blue space 1.5±5.7%; residential gardens 25.2±17.1%; green space with gardens (*Green*) 67.45±19.72%; green space, residential gardens and blue space (*Green/Blue*) 69.0±19.7%. All-cause mortality reduced with increasing natural environment density in unadjusted and fully adjusted models (Table 1). The association was slightly stronger for *Green* compared with *Green/Blue* (i.e., when blue space was excluded). Income-stratified analysis showed that SMR and natural environment were only significantly negatively associated for areas within the most income deprived tertile (Figure 1; Table 2).

**Prescribing and natural environment**

Across the LSOAs, over 210 million items were prescribed for cardiovascular conditions in 2011 (210,694,436), with a mean of 6,523±3,271 per LSOA, at a total cost of over £896 million (£896,359,478) or £27,753±11,964 per LSOA. Equivalent figures for anti-depressants were 33,020,012 prescriptions in total (1,021±512 per LSOA) at a total cost of £176,620,083 (5,470±2,549 per LSOA).

Unadjusted models for both cardiovascular conditions and anti-depressants indicated that prescribing volume and associated cost were *higher* in areas with higher *Green/Blue* natural environment density, although for anti-depressant prescribing outcomes, this was not statistically significant for all natural environment categories (Table 1). In adjusted models, associations remained in the same direction for cardiovascular prescribing, and were significant for the some natural environment categories; for volume (≥75% vs. <25% *Green/Blue*) and cost (50-74.9% and ≥75% vs. <25% *Green/Blue*). For anti-depressant prescribing, the direction of the associations was reversed, such that volume and costs were *lower* in areas with higher natural environment density, but associations were not statistically significant for *Green/Blue* or *Green*.

In income-stratified analysis, some of the positive associations between natural environment (*Green/Blue*) and cardiovascular prescribing volume and cost remained significant, but only for areas in income tertiles 2 and 3 for volume, and in tertile 1 for cost (Table 2). For anti-depressant prescribing, the expected negative association was evident (with the exception of prescribing cost in income tertile 1), but did not reach significance.

## DISCUSSION

We present novel analysis of national prescribing data for England in to relation natural environment exposure, including public green space, private gardens and blue space. There were contrasting associations of areas with higher density of natural environment having significantly higher prescribing for cardiovascular conditions, but non-significant trend towards lower prescribing of anti-depressants. The significant pattern of lower all-cause mortality in areas with higher area density of natural environment, which was slightly stronger when blue space was excluded, was consistent with previously reported area-level relationships for urban green space (excluding private gardens and blue space). So too was the apparently stronger protective relationship between natural environment and all-cause mortality in the most deprived areas (Maas et al., 2006; Mitchell & Popham, 2008). Income stratified analysis with the prescribing data did not produce such consistent patterns.

Our lack of significant associations between natural environment and anti-depressant prescribing are not in keeping with epidemiological evidence linking greener living environments with better mental health (Triguero-Mas et al., 2015; Wheeler et al., 2012; White et al., 2013); evidence that supports the notion of stress relief and restoration as mechanisms through which natural environments confer health benefit. This could raise questions about the use of anti-depressant prescribing as a proxy for general mental health in ecological analysis. However, Nutsford et al. (2013) reported some significant relationships from analysis of individual-level prescribing anxiety/mood disorders in Auckland (New Zealand). Prescribing was associated with total green space within 3 km (IRR= .956, 95%CI .943-.970), the proportion of useable green space within 3 km (IRR=.964, 95%CI .950-0.979), and distance to nearest useable green space (IRR=1.352, 95%CI 1.024-1.785). Overall the amount of both total and useable green space within 3 km, and distance to nearest useable green space, appeared to have a protective effect. It is possible that differences in prescribing data explain why our results differ. For example, the New Zealand data allowed individual-level age-standardisation, which was only possible for mortality in the present analyses (where the expected relationship was observed). The study of antidepressant prescriptions and street trees in London showed that greater density of street trees was associated with slightly fewer prescriptions of antidepressants (-1.18 prescriptions per thousand per tree/km, 95% credibility interval -2.45, 0.00) (Taylor et al., 2015). But the authors advocated caution given the small number of large areal units involved; 33 boroughs, with a mean population of 250,000 (compared with 32,250 LSOAs, with a mean population of 1600 in our dataset).

Cardiovascular prescribing has not previously been explored in relation to green space. Studies reporting cardiovascular health outcomes have found lower incidence or risk in more natural areas (Richardson & Mitchell, 2010; Tamosiunas et al., 2014), but a lack of association has been reported in other area-level analysis (Richardson, Pearce, Mitchell, Day, & Kingham, 2010). Our finding of a small, but significant association of higher cardiovascular prescribing in areas with higher natural environment density was contrary to expectation. It could, therefore, reflect the difficulties of detecting associations using small area-level analyses. It could also be a reflection of the generally lower support for natural environments having protective effects for cardiovascular health (e.g., through facilitating physical activity), compared more commonly evidenced psychological and mental health benefits.

Based on the few prescribing studies and the broader epidemiological evidence, it is perhaps not surprising that there was no evidence of a protective relationship between natural environment and cardiovascular prescribing. Anti-depressant prescribing was a stronger candidate for exploration, showed non-significant associations in the expected direction, and warrants further attention, in addition to considering other conditions (e.g., respiratory disease). One of the attractions of using prescribing data in this area is the ease with which prescribing cost data can be used and interpreted. For example, based on mean antidepressant cost per LSOA of £5,470 over 12 months, a 2.9% lower cost of anti-depressant prescribing in areas with ≥75% *Green* natural environment coverage (based on IRR of .971 compared with areas of <25%; Table 1) equates to a difference of £159 per LSOA (), or £5.12 million across the 32,250 LSOA nationally. In the absence of significant findings, we are not able to make such assertions, but advocate further exploration focusing where the biologically plausible links are strongest, which might include prescribing for other mental health conditions and respiratory diseases.

The strengths of this study include, first, the use of national data at small area-level, compared with other UK studies of wards or boroughs and on a national scale, compared with city-level. Second, we considered natural environment using broad definitions, rather than delimiting to urban green space, and checked the concurrent validity against all-cause mortality before exploratory analysis with prescribing data. Third, the inclusion of both volume and cost of prescribing would allow for tangible interpretation of the financial implications of associations. Fourth, analysis adjusted for a range of other possible area-level confounders and other random area-level effects.

This study is subject to limitations common to small-area, ecological analyses, such as the inability to infer causality and the ecological fallacy (one cannot assume that area-level associations exist at individual-level). The limitation of UK prescribing data being released at the level of GP catchment areas and the challenge of aligning these data with standard geographical units, such as LSOAs, is perhaps the most difficult overcome, although our methods appeared to perform well. The associated inability to age-sex standarise prescribing data at individual-level (as we could for mortality) might have been a limiting factor, although we did include area-level confounder variables to account for differences in area population profiles. The cardiovascular prescribing category comprises 13 sub-categories, which might be too broad to identify links to environment and specific medication types might be more appropriate if specific conditions are of interest. Similarly, even within single medication types, such as anti-depressants, there is scope to identify specific drugs for analysis. Although not feasible here, this additional processing could afford the sensitivity required to detect associations and better understand cost implications. Finally, our natural environment indicator did not allow us to unpick possible effects based on natural environment type or quality (Wheeler et al., 2015).

**Conclusion**

Our data suggest that higher density of natural environment in an area (including public green space, private gardens and blue space) is not association with lower volume or cost of anti-depressant or cardiovascular prescribing, but is associated with lower all-cause mortality. The use of prescribing data as proxy health indicators warrants further examination.

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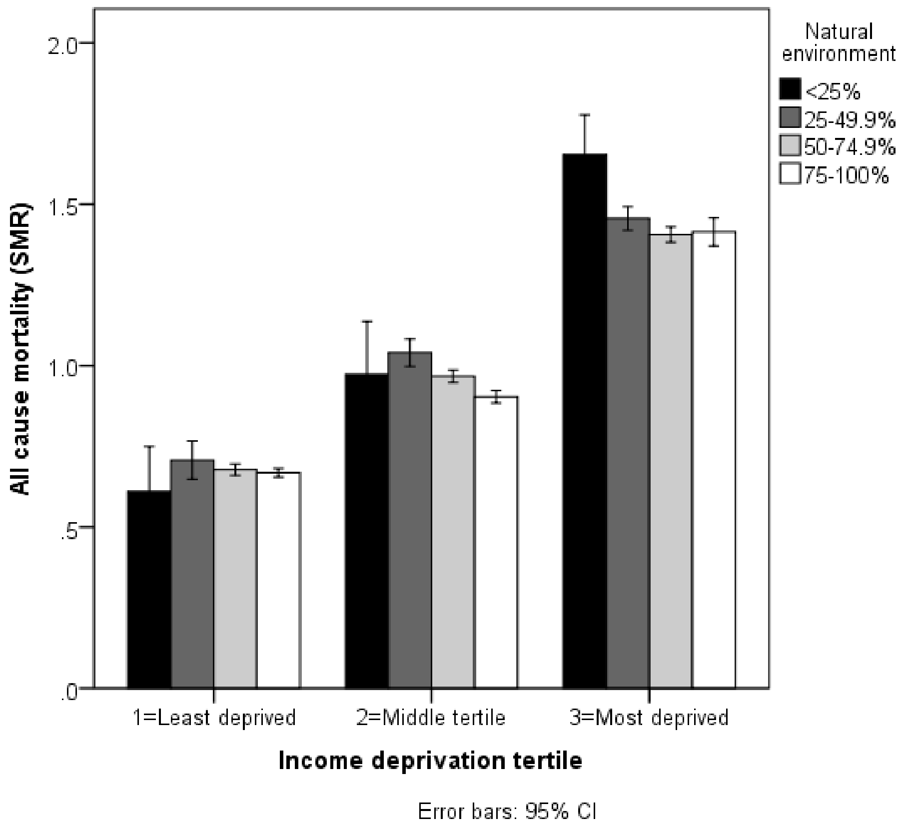


Figure 1. All-cause mortality by natural environment categories, across income deprivation tertiles

Table 1. Poisson regression coefficients for unadjusted and adjusted models (statistically significant figures in **bold**)

| | Natural environment (%) | *Green/Blue* [a] | | | *Green/Blue* [b] | | | *Green* [b] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | IRR | 95% Credibility Interval | | IRR | 95% Credibility Interval | | IRR | 95% Credibility Interval | |
| Cardiovascular prescribing - volume | <25% | ref | | | | | | | | |
| | 25-49.9% | **1.085** | **1.021** | **1.155** | 1.037 | 0.976 | 1.103 | 1.019 | 0.969 | 1.072 |
| | 50-74.9% | **1.144** | **1.076** | **1.218** | 1.052 | 0.988 | 1.120 | 1.024 | 0.973 | 1.079 |
| | >75% | **1.232** | **1.158** | **1.312** | **1.090** | **1.023** | **1.162** | **1.056** | **1.002** | **1.114** |
| Cardiovascular prescribing - cost | <25% | ref | | | | | | | | |
| | 25-49.9% | **1.072** | **1.037** | **1.108** | 1.032 | 0.998 | 1.067 | 1.024 | 0.997 | 1.053 |
| | 50-74.9% | **1.101** | **1.064** | **1.139** | **1.035** | **1.000** | **1.071** | 1.025 | 0.997 | 1.054 |
| | >75% | **1.113** | **1.076** | **1.152** | **1.040** | **1.005** | **1.077** | 1.028 | 0.999 | 1.059 |
| Anti-depressant prescribing - volume | <25% | Ref | | | | | | | | |
| | 25-49.9% | 1.040 | 0.911 | 1.195 | 0.981 | 0.859 | 1.126 | 0.966 | 0.865 | 1.083 |
| | 50-74.9% | 1.131 | 0.993 | 1.296 | 0.954 | 0.836 | 1.096 | 0.933 | 0.835 | 1.045 |
| | >75% | **1.225** | **1.075** | **1.405** | 0.997 | 0.870 | 1.148 | 0.969 | 0.865 | 1.090 |
| Anti-depressant prescribing - cost | <25% | Ref | | | | | | | | |
| | 25-49.9% | 1.050 | 0.987 | 1.118 | 0.989 | 0.931 | 1.052 | 0.974 | 0.925 | 1.025 |
| | 50-74.9% | **1.113** | **1.047** | **1.185** | 0.977 | 0.918 | 1.040 | 0.958 | 0.909 | 1.009 |
| | >75% | **1.140** | **1.071** | **1.214** | 0.993 | 0.931 | 1.058 | 0.971 | 0.920 | 1.024 |
| SMR all-cause [c] | | | | | | | | | | |
| | <25% | ref | | | | | | | | |
| | 25-49.9% | **0.882** | **0.790** | **0.989** | 0.944 | 0.844 | 1.061 | 0.927 | 0.841 | 1.024 |
| | 50-74.9% | **0.736** | **0.661** | **0.824** | **0.882** | **0.785** | **0.996** | **0.858** | **0.776** | **0.952** |
| | >75% | **0.607** | **0.543** | **0.681** | **0.877** | **0.773** | **0.999** | **0.825** | **0.737** | **0.927** |

[a] Unadjusted
[b] Adjusted for deprivation in education, skills, and training; deprivation in the living environment; urban-rural classification; ethnicity; proportion of the LSOA population aged 20-64, and ≥65 yr (prescribing data only)
[c] zeroinflated poisson regression

Table 2. Poisson regression coefficients for adjusted models stratified by income tertile (statistically significant figures in **bold**)

| | Natural environment (*%Green/Blue*) | **Income Deprivation Tertile** **1** (least deprived) IRR | 95% Credibility Interval | | **2** IRR | 95% Credibility Interval | | **3** (most deprived) IRR | 95% Credibility Interval | |
|---|---|---|---|---|---|---|---|---|---|---|
| Cardiovascular prescribing - volume [a] | <25% | ref | | | | | | | | |
| | 25-49.9% | 0.976 | 0.771 | 1.253 | 1.086 | 0.940 | 1.261 | 1.047 | 0.979 | 1.122 |
| | 50-74.9% | 1.164 | 0.921 | 1.491 | **1.162** | **1.006** | **1.349** | 1.041 | 0.971 | 1.117 |
| | >75% | 1.224 | 0.967 | 1.570 | **1.198** | **1.035** | **1.393** | **1.081** | **1.004** | **1.165** |
| Cardiovascular prescribing - cost [a] | <25% | ref | | | | | | | | |
| | 25-49.9% | 1.053 | 0.927 | 1.197 | 1.029 | 0.951 | 1.115 | 1.043 | 1.004 | 1.083 |
| | 50-74.9% | **1.162** | **1.022** | **1.323** | 1.074 | 0.991 | 1.164 | 1.032 | 0.993 | 1.074 |
| | >75% | **1.179** | **1.036** | **1.342** | 1.077 | 0.993 | 1.169 | 1.036 | 0.994 | 1.080 |
| Anti-depressant prescribing - volume [a] | <25% | ref | | | | | | | | |
| | 25-49.9% | 0.883 | 0.535 | 1.576 | 0.952 | 0.702 | 1.331 | 0.980 | 0.842 | 1.149 |
| | 50-74.9% | 0.938 | 0.576 | 1.657 | 0.952 | 0.705 | 1.327 | 0.919 | 0.789 | 1.079 |
| | >75% | 0.968 | 0.593 | 1.715 | 0.983 | 0.725 | 1.376 | 0.963 | 0.818 | 1.141 |
| Anti-depressant prescribing - cost [a] | <25% | ref | | | | | | | | |
| | 25-49.9% | 0.934 | 0.757 | 1.164 | 0.929 | 0.814 | 1.066 | 0.994 | 0.926 | 1.067 |
| | 50-74.9% | 1.014 | 0.824 | 1.261 | 0.954 | 0.836 | 1.094 | 0.952 | 0.886 | 1.025 |
| | >75% | 1.040 | 0.844 | 1.295 | 0.969 | 0.848 | 1.114 | 0.969 | 0.897 | 1.047 |
| SMR all-cause [b] | | | | | | | | | | |
| | <25% | ref | | | | | | | | |
| | 25-49.9% | 1.367 | 0.629 | 3.704 | 0.962 | 0.690 | 1.401 | 0.900 | 0.800 | 1.019 |
| | 50-74.9% | 1.207 | 0.560 | 3.256 | 0.940 | 0.672 | 1.376 | **0.777** | **0.686** | **0.885** |
| | >75% | 1.146 | 0.526 | 3.116 | 0.917 | 0.648 | 1.355 | **0.792** | **0.690** | **0.912** |

[a] Adjusted for: deprivation in education, skills, and training; deprivation in the living environment; urban-rural classification; ethnicity; proportion of the LSOA population aged 20-64, and ≥65 yr (prescribing data only)
[b] zeroinflated poisson regression