Are primary care factors associated with hospital episodes for adverse drug reactions? A national observational study

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ABSTRACT

Objective: Identification of primary care factors associated with hospital admissions for adverse drug reactions (ADRs).


Method: We identified all hospital episodes with an International Classification of Diseases (ICD) 10 code indicative of an ADR, in the 2010–2012 English Hospital Episode Statistics (HES) admissions database. These episodes were linked to contemporary data describing the associated general practice, including general practitioner (GP) and patient demographics, an estimate of overall patient population morbidity, measures of primary care supply, and Quality and Outcomes Framework (QOF) quality scores. Poisson regression models were used to examine associations between primary care factors and ADR-related episode rates.

Results: 212 813 ADR-related HES episodes were identified. Rates of episodes were relatively high among the very young, older and female subgroups. In fully adjusted models, the following primary care factors were associated with increased likelihood of episode: higher deprivation scores (population attributable fraction (PAF)=0.084, 95% CI 0.067 to 0.100) and relatively poor glycated haemoglobin (HbA1c) control among patients with diabetes (PAF=0.372; 0.218 to 0.496). The following were associated with reduced episode likelihood: lower GP supply (PAF=−0.016; −0.026 to −0.005), a lower proportion of GPs with UK qualifications (PAF=−0.035; −0.058 to −0.012), lower total QOF achievement rates (PAF=−0.021; −0.042 to 0.000) and relatively poor blood pressure control among patients with diabetes (PAF=−0.144; −0.280 to −0.022).

Conclusions: Various aspects of primary care are associated with ADR-related hospital episodes, including achievement of particular QOF indicators. Further investigation with individual level data would help develop understanding of the associations identified. Interventions in primary care could help reduce the ADR burden. ADRs are candidates for primary care sensitive conditions.

Strengths and limitations of this study

We analysed recent data with national coverage.

Practice-specific data were available for all predictors.

The analysis was cross-sectional and at practice-level. We can therefore neither infer that the observed associations are causally linked, nor that they persist at the individual level.

We were unable to directly adjust for prescribing burden.

INTRODUCTION

Adverse drug reactions (ADRs) have been described as the undesirable and unintended effects of drugs further to their anticipated therapeutic impact, at usual therapeutic doses.1 They may be predictable or unpredictable, and acceptable or not.2 Occurrence is influenced by local practice,3 including prescribing systems,4 drug monitoring and associated systems,5 6 drug interactions and polypharmacy,7 8 and individual patient characteristics.3 They are caused by both over-the-counter and prescription medications.9 They are a major source of iatrogenic harm, and associated with excess morbidity and mortality.10 A 2002 review suggested approximately 7% of UK emergency hospital admissions and 4 in 100 UK hospital bed-days are associated with ADRs.11 Unadjusted numbers of ADR-related admissions have been increasing since the late 1990s, with rates of increase exceeding those for hospital admissions per se.12 13 Enhanced reporting,14 population ageing, increasing comorbidity and polypharmacy15 are likely to have contributed to these upward trends. The economic cost of these admissions and some other aspects of ADR management was estimated at £750 million per year in 2006.16

A recent meta-analysis concluded that approximately half of the ADRs identified in secondary care are preventable. However, identifying interventions with consistent positive impact on prescribing errors or ADRs has been difficult. Studies linking both prescribing habits and hospital admissions for particular conditions with primary care provision and performance, nevertheless, indicate that modifiable aspects of primary care influence ADR and hospital admission rates. For example, two recent analyses of primary care data support a negative correlation between prescribing errors, and both, practice list size and designation, as a training versus non-training practice. General practitioner (GP) age, sex, handedness of practice and list size have also been linked to ADR reporting (potentially a proxy for pharmacovigilance more generally), and list size, GP supply and country of qualification with admission rates, for several other particular conditions.

Quality and Outcomes Framework (QOF) performance, on both clinical and service access indicators, has been linked to admission rates for various conditions.

To further assess the extent to which ADRs might be influenced by primary care, we have here considered, at practice level, associations between ADR-related admissions and practice demographics, patient factors, measures of primary care supply and performance indicators. We hypothesised that lower ADR admission rates would be associated with higher resourcing and performance measures.

METHODS

Ethics statement

This was a secondary use of administrative data. The only patient-level data used were Hospital Episode Statistics (HES) data provided by the Health and Social Care Information Centre (HSCIC). The remainder of the data were publicly available practice-level data from the HSCIC (http://www.hscic.gov.uk/home). This is also the case with other published UK analyses that have used HES data.

Study design, data sources and variables

We performed a cross-sectional analysis of 2010–2012 hospital and primary care data from England.

Outcome data

The admissions data used to generate our outcome variable were extracted from the 2010 to 2012 English HES Admitted Patient Care data. All episodes of in-hospital care delivered in National Health Service (NHS) hospitals or funded by the NHS are included in this data set. This covers the vast majority of emergency admissions. Accident and emergency attendances without subsequent admission are not included. Each database entry (‘episode’) corresponds to an uninterrupted period of care under a particular hospital consultant. A single inpatient admission in one hospital trust (a HES ‘spell’) can therefore include more than one episode. Duplicate entries (0.026% of total) were excluded. National audit of HES admissions data has shown that 89% of primary diagnoses are valid.

We defined ADR-associated episodes as those with an International Classification of Diseases (ICD) 10 diagnosis term containing the terms, ‘drug-induced’, ‘due to [drug]’, ‘induced by [drug]’, ‘adverse effect of correct drug’, or ‘adverse event of drug’. Those with diagnoses of ‘malignant neuroleptic syndrome’, ‘ototoxic hearing loss’, ‘toxic liver disease’, ‘toxic epidermal necrolysis’, ‘drug phototoxic response’, ‘drug photoallergic response’, ‘post-immunisation arthropathy’, ‘complications following infusion, transfusion and therapeutic injection’ and ‘infection following immunisation’, were also included, as were those with a diagnosis field containing an ‘external cause’ code between Y40 and Y59, which indicate that a drug is the expected cause of a particular diagnosis. Drug-associated poisoning was excluded. An exhaustive list of eligible ICD-10 codes is available as online supplementary file S1. We used the general practice linked to each of the included HES episodes to calculate numbers of ADR-associated episodes per practice.

Predictor variables: practice demographics and performance measures

Various practice demographic and performance measures were used as predictor variables. Data were obtained from the HSCIC. The following predictors were generated from the 2012 General and Personal Medical Services Data.

Continuous

1. Practice list size
2. GP supply: number of full-time equivalent (FTE) GPs/1000 patients
3. Per cent of GPs ≥50 years
4. Per cent of female GPs
5. Per cent of GPs with non-UK primary medical qualifications

Binary


The practitioner-related data accounted for all GP providers, salaried/other GPs, GP retainers and GP registrars. Overall 2011–2012 practice QOF performance (per cent of maximum score of 1000 points achieved), and the following 2011–2012 QOF clinical and medication management indicators were identified as additional predictors:

1. Clinical indicators (as markers for overall clinical quality of care)
   A. CHD06: The percentage of patients with coronary heart disease in whom the last blood pressure reading (measured in the preceding 15 months) is 150/90 or less
   B. CHD08: The percentage of patients with coronary heart disease whose last measured total cholesterol
(measured in the preceding 15 months) is 5 mmol/L or less;

C. STROKE06: The percentage of patients with a history of transient ischaemic attack (TIA) or stroke in whom the last blood pressure reading (measured in the preceding 15 months) is 150/90 mm Hg or less;

D. STROKE08: The percentage of patients with TIA or stroke whose last measured total cholesterol (measured in the preceding 15 months) is 5 mmol/L or less;

E. DM17: The percentage of patients with diabetes whose last measured total cholesterol within the preceding 15 months is 5 mmol/L or less;

F. DM26: The percentage of patients with diabetes in whom the last International Federation of Clinical Chemistry (IFCC)-glycated haemoglobin (HbA1c) is 59 mmol/mol (equivalent to HbA1c of 7.5% in Diabetes Control and Complications Trial units) or less (or equivalent test/reference range depending on local laboratory) in the preceding 15 months;

G. DM30: The percentage of patients with diabetes in whom the last blood pressure is 150/90 or less;

H. BP05: The percentage of patients with hypertension in whom the last blood pressure (measured in the preceding 9 months) is 150/90 mm Hg or less.

2. Medication management (both binary indicators)

A. MEDICINES12: A medication review is recorded in 2010–2011 QOF patient experience indicator data for repeat medicines, standard 80%;

B. RECORDS09: For repeat medicines, an indication for the drug can be identified in the records (for drugs added to repeat prescriptions with effect from 2 April 2004), minimum standard 80%.

These particular clinical indicators were selected as they are important indicators related to common conditions relevant to all practices. They apply disproportionately to older age groups and those with multimorbidity (among whom the targets will be more challenging to meet), and reflect the need for long-term monitoring, which can also be difficult to achieve. The 2010–2011 QOF patient experience indicator data were used, as these indicators were dropped in 2011–2012:

1. PE07: Patient experience of access (1). The percentage of patients who, in the GP Patient Survey, indicate that they were able to obtain a consultation with a GP within two working days. (NB: The GP Patient Survey is a national survey run by an independent survey agency for the NHS. 1.4 million adult patients registered with a GP in England are sampled 4x/year. Almost 2 million responses were received in 2010–2011; response rate=36%.)

2. PE08: Patient experience of access (2). The percentage of patients who, in the appropriate national survey, indicate that they were able to book an appointment with a GP more than two days ahead.

Predictor variables: patient population sociodemographic and comorbidity data

Covariates included descriptors of practice populations. The age and gender distributions of each practice population (at 2011), and their Index of Multiple Deprivation (IMD) scores (from 2010), were obtained from the HSCIC Indicator Portal. The following variables were produced with these data:

1. Age group (categorical variable using Office for National Statistics (ONS) age-bands);
2. Sex (male/female binary variable);
3. IMD score (continuous variable).

A summary practice population ethnicity variable was produced using 2011 ONS Census data. The ethnicity categories were collapsed into a ‘per cent white’ variable (per cent belonging to any of the English/Welsh/Scottish/Northern Irish/British, Irish, Gypsy or Irish Traveller or Other White groups).

As disease burden is associated with rates of admissions, prescribing burden and ADRs, a practice morbidity variable was produced by totalling the numbers of practice QOF disease registrations (2011–2012) for coronary heart disease, heart failure, stroke/TIA, hypertension, atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease, asthma, epilepsy, hypothyroidism, cancer, palliative care, schizophrenia, bipolar disorder, other psychoses, depression and dementia, and expressing this as a proportion of list size. Comparison with the Charlson Index has indicated that QOF registration data can reasonably estimate morbidity.

Exclusions

Practices for which a patient count was not available (n=153), with an incomplete set of predictors (n=538) and/or with a list size <500 (n=3), were excluded from analysis.

Statistical analysis

For each combination of practice, sex and age group, we computed a count of total ADR-related HES episodes for 2010–2012, and fitted Poisson general estimating equation (GEE) regression models to these data, using Huber variances clustered by practice, with an exposure variable equal to the number of patients in that practice with that gender and age group. For estimating crude rates by gender and age group, we used GEEs with zero correlation. For estimating effects of practice-level predictors, we used GEEs with exchangeable correlation. The parameters of the practice-effects models were a base ADR rate for each combination of gender and age group, and rate ratios corresponding to practice-specific risk factors, which were constant within each practice. For each risk factor, we fitted an unadjusted model, the parameters of which were the base ADR rates and risk ratios for that factor, using binary indicators for binary factors and the quadratic reference-spline method for continuous factors. We then fitted an adjusted model, containing the base rates and rate ratios for all the risk factors.
factors. For each factor (continuous or binary), we estimated the adjusted and unadjusted population attributable fraction (PAF), comparing ADR rates between the real-world scenario and a hypothetical scenario where that factor was at the base level for all participants. Table 1 displays the baseline and other reference points for all predictors. The reference-spline models used allow the real world to be compared with a hypothetical scenario, in which all practices had the baseline level of a continuous covariate. The PAF is then the proportion of ADRs attributable to living in the real world, instead of in the hypothetical scenario. For instance, in the case of GP supply (FTE/1000 patients), the real world is compared to a hypothetical scenario, in which each practice had 7.5 FTEs per 1000 patients. Analyses were carried out using V13.1 of Stata statistical software.

**RESULTS**

**Summary statistics**

After removal of duplicates, 212,813 ADR-related HES episodes were identified. Following practice exclusions (as above), 7664 (91.7% of 8358) practices remained, with 53,422,119 registered patients. These included practices that were associated with 201,246 (94.6%) of the identified HES episodes; 72.1% of these episodes (n=145,077) were discrete admissions to an NHS Trust (ie, did not occur within the same HES spell). Table 2 displays the number of episodes containing ADR-related ICD-10 codes, by ICD-10 chapter. Most episodes were identified by an ‘external cause’ code, as anticipated in view of the limited number of primary diagnosis codes that attribute a diagnosis to a drug. It is likely that some episodes had both, diagnosis and external cause codes, indicative of an ADR, as the information each provides (disease attributed to drug, and drug considered responsible, respectively), is different. It is also possible that some individuals received more than one ADR diagnosis.

Practice admission and demographic characteristics, the nature of their patient populations and their QOF performance outcomes, are summarised in table 3. Clustering around high levels of achievement was apparent for many of the QOF outcomes.

Table 4 displays ADR-related episode rates by patient age and sex. Relatively high rates were apparent in the very young and older age groups. Post 0–4 years (for whom rates=0.76/1000 person-years, 95% CI 0.70 to 0.81), rates increased with age, from 0.37 (0.34 to 0.40) per 1000 person-years among the 5–14 years age group, to 12.3 (11.9 to 12.6) per 1000 person-years among the ≥85 years age group. Rates were also higher among females compared with males: 2.10 (2.06 to 2.14) vs 1.66 (1.63 to 1.70) per 1000 person-years, respectively.

**ADR episodes and practice characteristics**

The regression analysis outcomes are reported as unadjusted and adjusted PAFs (table 5). These describe, for each predictor, the proportional difference in ADR-related episode rates associated with the difference between the reference scenario for that variable (baseline in table 1) and the sample scenario. The unadjusted and adjusted incidence rate ratios associated with each of the reference points for each factor (as per table 1) are reported in online supplementary file S2. In fully adjusted models, the following factors were associated with increased likelihood of ADR-related episode: higher deprivation scores, higher GP supply, a higher proportion of GPs with UK qualifications, higher total QOF achievement scores, lower performance on QOF indicator DM26 (ie, relatively poor HbA1c control among patients with diabetes) and higher performance on indicator DM30 (ie, relatively good blood pressure control among patients with diabetes). Examination of the rate ratios corresponding to HES episode rates in the scenarios where either 50% or 100%—vs 0%—of GPs held non-UK qualifications, however, suggested a non-linear association between ADR-related episodes and country of qualification (adjusted rate ratio (ARR) for 50% vs 0%=0.92 (95% CI 0.88 to 0.97; p=0.0025), whereas ARR for 100% vs 0%=0.97 (0.91 to 1.04);
Additionally, the rate ratio corresponding to the episode rates in the scenario where binary QOF indicator RECORD09 was universally not achieved, compared with universally achieved, was indicative of a bottom-end negative association between indicator achievement (drug indications noted in patient records) and episode rates (ARR for indicator non-achievement vs achievement=1.08 (1.00 to 1.16); p=0.046).

## DISCUSSION

### Summary of results

We aimed to investigate associations between ADR-related HES episodes and various aspects of primary care, including performance, in an observational study of 2010–2012 data. In our sample, the number of ADR-related episodes, and their distribution by population age and sex, was consistent with previous studies. Higher deprivation scores, higher GP supply, a
higher proportion of GPs with UK qualifications, high total QOF achievement, relatively poor HbA1c control among patients with diabetes, relatively good blood pressure control among patients with diabetes and potentially lower recording of drug indications in patient records, were positively associated with increased likelihood of ADR-related episodes.

Comparison with the existing literature

The association between ADR-related episodes and country of medical qualification was non-linear, and potentially spurious in a context of multiple comparisons and likely residual confounding. Country of qualification has previously been associated with unplanned cancer admissions, but in that case, non-UK qualification was associated with increased likelihood of admission.27 Similar variety in direction of effect on admission rates has been observed for GP supply. Where positive correlations between supply and admissions have been observed (as here, and previously for stroke admissions25), this could potentially reflect a loss of continuity of care due to care for individual patients being shared by a larger number of GPs. It is also plausible that more GPs per patient would enhance rates of identification and reporting of ADRs, rather than ADR occurrence. It is difficult to imagine that more GPs would have a negative impact on ADR episode rates per se.

The observed effect of deprivation is in keeping with its consistent positive association with emergency admission rates—both generally, and for various specific conditions, including ADRs.27 40–42 Further studies have linked lower socioeconomic status with greater polypharmacy, higher prescription rates for drugs commonly implicated in ADRs and higher drug dosage,43 44 with dosage reportedly higher despite adjustment for multimorbidity.

We are cautious about the apparent association between higher total QOF achievement and ADR episodes in view of the small effect size, multiple comparisons and a high degree of clustering around high achievement. High total QOF achievement has previously been associated with a reduced likelihood of admission for both cancer and angina.26 45 This is not necessarily out of keeping with our observation, however, as many QOF indicators are directly or indirectly associated with prescribing. That is, prescribing burden may be part of the apparent effect of overall

<table>
<thead>
<tr>
<th>Table 3 Practice characteristics</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HES episodes associated with ADRs (total count 2010–2012)</td>
<td>19</td>
<td>7–38</td>
</tr>
<tr>
<td>Patient age (% &gt;65 years)</td>
<td>16.0</td>
<td>11.8–19.5</td>
</tr>
<tr>
<td>Patient sex (% female)</td>
<td>50.3</td>
<td>49.0–51.2</td>
</tr>
<tr>
<td>Patient ethnicity (% white)</td>
<td>92.8</td>
<td>76.5–97.2</td>
</tr>
<tr>
<td>Patient morbidity score (registrations/1000 patients)</td>
<td>500.4</td>
<td>424.8–568.8</td>
</tr>
<tr>
<td>IMD</td>
<td>21.7</td>
<td>13.7–32.0</td>
</tr>
<tr>
<td>Practice characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Practice list size (1000s)</td>
<td>6.2</td>
<td>3.7–9.4</td>
</tr>
<tr>
<td>GP supply (FTE/1000 patients)</td>
<td>6.0</td>
<td>4.9–7.5</td>
</tr>
<tr>
<td>Handedness of practice (% single-handed)</td>
<td></td>
<td>10.2</td>
</tr>
<tr>
<td>GPs &gt;50 years (%)</td>
<td>40.0</td>
<td>22.2–60.0</td>
</tr>
<tr>
<td>Female GPs (%)</td>
<td>50.0</td>
<td>33.3–60.0</td>
</tr>
<tr>
<td>GPs with non-UK qualifications (%)</td>
<td>20.0</td>
<td>0.0–50.0</td>
</tr>
<tr>
<td>QOF indicator achievement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total QOF points (%)</td>
<td>98.6</td>
<td>96.8–99.4</td>
</tr>
<tr>
<td>PE07 (%)</td>
<td>84.4</td>
<td>76.8–91.1</td>
</tr>
<tr>
<td>PE08 (%)</td>
<td>77.8</td>
<td>66.5–87.5</td>
</tr>
<tr>
<td>CHD06 (%)</td>
<td>90.6</td>
<td>87.7–93.3</td>
</tr>
<tr>
<td>CHD08 (%)</td>
<td>80.2</td>
<td>75.9–84.5</td>
</tr>
<tr>
<td>STROKE06 (%)</td>
<td>89.2</td>
<td>85.5–92.3</td>
</tr>
<tr>
<td>STROKE08 (%)</td>
<td>77.8</td>
<td>72.4–82.5</td>
</tr>
<tr>
<td>DM17 (%)</td>
<td>81.9</td>
<td>77.8–85.6</td>
</tr>
<tr>
<td>DM26 (%)</td>
<td>70.2</td>
<td>65.0–75.1</td>
</tr>
<tr>
<td>DM30 (%)</td>
<td>90.4</td>
<td>87.4–93.2</td>
</tr>
<tr>
<td>BP05 (%)</td>
<td>80.3</td>
<td>76.2–84.0</td>
</tr>
<tr>
<td>MED12 (% of practices achieving target)</td>
<td></td>
<td>96.8</td>
</tr>
<tr>
<td>RECORD09 (% of practices achieving target)</td>
<td></td>
<td>93.5</td>
</tr>
</tbody>
</table>

Median and IQR for continuous variables, and percentage of practices single-handed, and achieving QOF indicators MED12 and RECORD09, are displayed.

ADR, adverse drug reaction; FTE, full-time equivalent; GP, general practitioner; HES, Hospital Episode Statistics; IMD, Index of Multiple Deprivation; QOF, Quality and Outcomes Framework.
QOF achievement. The observed association between the DM30 blood pressure control indicator and ADR episodes provides an example of a target that may be associated with increased rates of ADRs, via higher prescribing rates. A recent meta-analysis suggested that relatively tight blood pressure control among those with diabetes is associated with higher risk of significant adverse events, although this was with control to lower levels than we have specifically investigated here. It is also possible that higher QOF achievement is reflective of relatively high-quality care in general, and thus, again, that this is associated with enhanced identification and reporting of ADRs, rather than ADR occurrence per se.

In contrast with blood pressure control, better HbA1c control was observed to be negatively associated with HES episode rates. Potentially relatively high HbA1c reflects treatment resistance, and higher levels of oral hypoglycaemic agent and insulin prescribing, which are known risk factors for ADR-related admissions. Reverse causality—whereby ADRs could impact on treatment adherence, or the treatment options available, and therefore QOF performance—may also be relevant. Although we did not observe a significant association between either of the medication management QOF indicators and episodes when considering PAFs, the rate ratios calculated did suggest a small negative association between recording of drug indications and ADR-related episodes. As the record-related data were binary and clustered at high levels, further study with data that provide more information would be of interest.

Strengths and limitations

Previous studies have considered associations between primary care factors and prescribing errors/high-risk prescribing, but so far as we are aware, this is the first study to investigate associations between primary care factors and ADR-related hospital episodes. The data available covered the majority of the English population, and we were able to control for important covariates. A limitation of the analysis was its cross-sectional and practice level nature, which means that we can infer neither causal links between the observed associations, nor individual level associations, and the ecological fallacy could operate. Additional limitations include the potential for inaccuracies and inconsistencies in the data sets used. HES data are based on patient notes and therefore reflect the quality of clinical record-keeping. Evidence from several reports suggests ADRs are under-reported and under-estimated in HES data, and therefore reflect the quality of clinical record-keeping. Additional limitations include the ecological fallacy, as potential for inaccuracies and inconsistencies in the data sets used. HES data are based on patient notes and therefore reflect the quality of clinical record-keeping. Evidence from several reports suggests ADRs are under-reported and under-estimated in HES data, and therefore reflect the quality of clinical record-keeping.

Table 4  ADR-related hospital episode rates by age and sex

<table>
<thead>
<tr>
<th>Age group</th>
<th>Males ADRs (1000s)</th>
<th>Person-years (1000s)</th>
<th>IR (95% CI)</th>
<th>Females ADRs (1000s)</th>
<th>Person-years (1000s)</th>
<th>IR (95% CI)</th>
<th>Pooled ADRs (1000s)</th>
<th>Person-years (1000s)</th>
<th>IR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>2.6</td>
<td>3288.4</td>
<td>0.78 (0.73 to 0.84)</td>
<td>2.3</td>
<td>3131.6</td>
<td>0.73 (0.64 to 0.82)</td>
<td>4.9</td>
<td>6420.0</td>
<td>0.76 (0.70 to 0.81)</td>
</tr>
<tr>
<td>5–14</td>
<td>2.5</td>
<td>6122.2</td>
<td>0.41 (0.36 to 0.46)</td>
<td>1.9</td>
<td>5838.0</td>
<td>0.33 (0.29 to 0.37)</td>
<td>4.4</td>
<td>11960.2</td>
<td>0.37 (0.34 to 0.40)</td>
</tr>
<tr>
<td>15–44</td>
<td>10.8</td>
<td>22199.5</td>
<td>0.49 (0.47 to 0.50)</td>
<td>16.5</td>
<td>21646.6</td>
<td>0.76 (0.74 to 0.78)</td>
<td>27.3</td>
<td>43846.1</td>
<td>0.62 (0.61 to 0.64)</td>
</tr>
<tr>
<td>45–64</td>
<td>22.5</td>
<td>13874.6</td>
<td>1.62 (1.55 to 1.70)</td>
<td>27.4</td>
<td>13494.8</td>
<td>2.03 (1.96 to 2.10)</td>
<td>49.9</td>
<td>27369.3</td>
<td>1.82 (1.77 to 1.88)</td>
</tr>
<tr>
<td>65–74</td>
<td>19.8</td>
<td>4394.8</td>
<td>4.51 (4.35 to 4.68)</td>
<td>20.2</td>
<td>4696.2</td>
<td>4.31 (4.19 to 4.43)</td>
<td>40.1</td>
<td>9091.0</td>
<td>4.41 (4.29 to 4.52)</td>
</tr>
<tr>
<td>75–84</td>
<td>21.0</td>
<td>2546.6</td>
<td>8.23 (8.00 to 8.46)</td>
<td>25.1</td>
<td>3265.5</td>
<td>7.68 (7.48 to 7.89)</td>
<td>46.0</td>
<td>5812.1</td>
<td>7.92 (7.75 to 8.10)</td>
</tr>
<tr>
<td>85+</td>
<td>9.4</td>
<td>768.4</td>
<td>12.24 (11.63 to 12.89)</td>
<td>19.4</td>
<td>1577.2</td>
<td>12.28 (11.95 to 12.61)</td>
<td>28.8</td>
<td>2345.6</td>
<td>12.27 (11.93 to 12.61)</td>
</tr>
<tr>
<td>Total</td>
<td>88.5</td>
<td>53194.4</td>
<td>1.66 (1.63 to 1.70)</td>
<td>112.7</td>
<td>53649.8</td>
<td>2.10 (2.06 to 2.14)</td>
<td>201.2</td>
<td>106844.2</td>
<td>1.88 (1.85 to 1.92)</td>
</tr>
</tbody>
</table>

The number of analysed person-years by combination of age group and sex, associated numbers of ADR-related episodes and corresponding incidence rates, is displayed. ADR, adverse drug reaction; IR, incidence rate.
also affects the practice handedness variable, which, in view of the contributions made by locum doctors, is likely to represent the management structure of the practice as much as the number of doctors it employs. We were constrained in looking at medical training, as further to those describing ‘non-UK qualification’, data are not easily available for use.

Regarding our definition of ADR-related episodes, we were unable to identify episodes that were unavoidable, due to over-the-counter medications, or to prescribing in secondary care. Moreover, we were unable to identify appropriate high-risk prescribing (ie, instances where the risk of ADR was known and accepted). It is not anticipated that these cases would be systematically associated with particular aspects of primary care in a large data set, but they may have limited the extent to which associations with primary care could be identified. We were also unable to adjust for prescribing burden directly, as we were unable to identify suitable data.

Implications for research and practice
We have previously suggested that observed associations between primary care factors and admissions for particular conditions support their classification as primary care sensitive conditions (PCSCs). PCSCs are defined as those conditions for which high-quality primary care can limit disease progression, complications and the need for secondary care. The concept has arisen in line with the pressures on primary care systems to limit hospital utilisation as demand has increased. However, there remains no widespread consensus on, or empirical basis for, criteria by which to identify PCSCs. ADRs have not typically been considered PCSCs, but our data indicate that they are likely sensitive to changes in primary care practice. Classifying ADRs as PCSCs could help encourage engagement with the issue, and allocate resources for investigation and implementation of strategies to reduce incidence, at the primary care level. Specific suggestions regarding strategies are difficult to make without further analyses to help understand some of the associations identified.

A particular issue raised by our analysis is the possibility that QOF targets may act to tip relatively high-risk prescribing decisions in favour of prescribing. This suggestion has been made previously, and previous
specific concerns about blood pressure targets have led the National Institute for Health and Care Excellence to apply age-caps to hypertension treatment targets, where evidence suggests treatment benefit is limited to certain age groups.24 Further investigation of the associations identified using individual level data, which would allow meaningful comparisons of effect size by age and ethnicity, would help to demonstrate if there are particular subgroups at risk of more harm than benefit in the pursuit of particular QOF targets. Consideration of ADRs subsequent to only specific drugs or drug classes would help to determine those implicated in the associations identified. Together, these pieces of information would help inform prescribing guidance that minimises potential prescribing-related harm.

CONCLUSIONS
ADR-related hospital episodes are associated with various primary care factors, including achievement of particular QOF indicators. Further investigation with individual level data, and analysis of both, population and ADR subgroups, would increase our understanding of these associations. ADRs are candidates for PCSCs.

Contributors AM, MS, RBN and AJM contributed to study design and interpretation of findings. Analyses were performed by RBN. All the authors contributed to drafting and revision of the report and approved the final version.

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Ethics approval The HSCIC provides ethical approval as part of the process of approving release of the HES data.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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REFERENCES


Diseases of the blood

D Diseases of the blood
D521 Drug-induced folate deficiency anaemia
D590 Drug-induced autoimmune haemolytic anaemia
D592 Drug-induced nonautoimmune haemolytic anaemia
D611 Drug-induced aplastic anaemia
Hypothyroidism due to medicaments and other exogenous substances
E032 Drug-induced thyroiditis
E160 Drug-induced hypoglycaemia without coma
E231 Drug-induced hypopituitarism
E242 Drug-induced Cushing’s syndrome
E273 Drug-induced adrenocortical insufficiency
E661 Drug-induced obesity
Mental and behavioural disorders due to use of sedatives or hypnotics
F13 Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances
F19 Malignant neuroleptic syndrome
G210 Other drug-induced secondary parkinsonism
G240 Drug-induced dystonia
G251 Drug-induced tremor
G254 Drug-induced chorea
G256 Drug-induced tics
G444 Drug-induced headache, not elsewhere classified
G620 Drug-induced polyneuropathy
G720 Drug-induced myopathy
H263 Drug-induced cataract
H910 Ototoxic hearing loss
Cardiomyopathy due to drugs and other external agents
I427 Hypotension due to drugs
I952 Acute drug-induced interstitial lung disorders
J702 Chronic drug-induced interstitial lung disorders
J703 Drug-induced interstitial lung disorders, unspecified
J704 Toxic liver disease
K71 Irritant contact dermatitis due to drugs in contact with skin
L233 Irritant contact dermatitis due to drugs in contact with skin
L244
L Diseases of the skin and subcutaneous tissue
  L251 Unspecified contact dermatitis due to drugs in contact with skin
  L270 Generalized skin eruptions due to drugs and medicaments
  L271 Localized skin eruptions due to drugs and medicaments
  L512 Toxic epidermal necrolysis (Lyell’s Syndrome)
  L560 Drug phototoxic response
  L561 Drug photoallergic response

M Diseases of the musculoskeletal system
  M022 Postimmunization arthropathy
  M102 Drug-induced gout
  M320 Drug-induced systemic lupus erythematosus
  M342 Systemic sclerosis induced by drugs and chemicals
  M804 Drug-induced osteoporosis with pathological fracture
  M814 Drug-induced osteoporosis without pathological fracture
  M835 Other drug-induced osteomalacia in adults
  M871 Osteonecrosis due to drugs

N Diseases of the genitourinary system
  N141 Nephropathy induced by other drugs, medicaments and biological substances
  N142 Nephropathy induced by unspecified drugs, medicaments and biological substances

T Injuries and consequences of external causes
  T805 Complications following infusion, transfusion and therapeutic injection: anaphylactic shock due to serum
  T806 Complications following infusion, transfusion and therapeutic injection: other serum reactions
  T808 Other complications following infusion, transfusion and therapeutic injection
  T809 Unspecified complication following infusion, transfusion and therapeutic injection
  T880 Infection following immunization
  T881 Infection complications following immunization
  T882 Shock due to anaesthesia
  T883 Malignant hyperthermia due to anaesthesia
  T886 Anaphylactic shock due to adverse effect of correct drug or medicament properly administered
  T887 Unspecified adverse event of drug or medicament
Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)

Y400  Penicillins

Y401  Cefalosporins and other beta-lactam antibiotics

Y402  Chloramphenicol group

Y403  Macrolides

Y404  Tetracycline

Y405  Aminoglycosides

Y406  Rifamycins

Y407  Antifungal antibiotics, systemically used

Y408  Other systemic antibiotics

Y409  Systemic antibiotic, unspecified

Y410  Sulfonamides

Y411  Antimycobacterial drugs

Y412  Antimalarials and drugs acting on other blood protozoa

Y413  Other antiprotozoal drugs

Y414  Anthelminthics

Y415  Antiviral drugs

Y418  Other specified systemic anti-infectives and antiparasitics
Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)

Y419 Systemic anti-infective and antiparasitic, unspecified

Y420 Glucocorticoids and synthetic analogues

Y421 Thyroid hormones and substitutes

Y422 Antithyroid drugs

Y423 Insulin and oral hypoglycaemic [antidiabetic] drugs

Y424 Oral contraceptives

Y425 Other estrogens and progestogens

Y426 Antagonadotrophins, antiestrogens, antiandrogens, not elsewhere classified

Y427 Androgens and anabolic congeners

Y428 Other and unspecified hormones and their synthetic substitutes

Y429 Other and unspecified hormone antagonists

Y430 Antiallergic and antiemetic drugs

Y431 Antineoplastic antimetabolites

Y432 Antineoplastic natural products

Y433 Other antineoplastic drugs

Y434 Immunosuppressive agents

Y435 Acidifying and alkalizing agents
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y436</td>
<td>Enzymes, not elsewhere classified</td>
</tr>
<tr>
<td>Y438</td>
<td>Other primarily systemic agents, not elsewhere classified</td>
</tr>
<tr>
<td>Y439</td>
<td>Primarily systemic agent, unspecified</td>
</tr>
<tr>
<td>Y440</td>
<td>Iron preparations and other anti-hypochromic-anaemia preparations</td>
</tr>
<tr>
<td>Y441</td>
<td>Vitamin B12, folic acid and other anti-megaloblastic-anaemia preparations</td>
</tr>
<tr>
<td>Y442</td>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Y443</td>
<td>Anticoagulant antagonists, vitamin K and other coagulants</td>
</tr>
<tr>
<td>Y444</td>
<td>Antithrombotic drugs [platelet-aggregation inhibitors]</td>
</tr>
<tr>
<td>Y445</td>
<td>Thrombolytic drugs</td>
</tr>
<tr>
<td>Y446</td>
<td>Natural blood and blood products</td>
</tr>
<tr>
<td>Y447</td>
<td>Plasma substitutes</td>
</tr>
<tr>
<td>Y449</td>
<td>Other and unspecified agents affecting blood constituents</td>
</tr>
<tr>
<td>Y450</td>
<td>Opioids and related analgesics</td>
</tr>
<tr>
<td>Y451</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Y452</td>
<td>Propionic acid derivatives</td>
</tr>
<tr>
<td>Y453</td>
<td>Other nonsteroidal anti-inflammatory drugs [NSAID]</td>
</tr>
<tr>
<td>Y454</td>
<td>Antirheumatics</td>
</tr>
</tbody>
</table>
Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y4554 Aminophenol derivatives

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y458 Other analgesics and antipyretics
Analgesic, antipyretic and anti-inflammatory drug, unspecified

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y459 Succinimides

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y460 Oxazolidinediones

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y461 Hydantoin derivatives

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y462 Deoxybarbiturates

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y463 Iminostilbenes

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y464 Valproic acid

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y465 Other and unspecified antiepileptics

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y466 Antiparkinsonism drugs

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y467 Antispasticity drugs

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y468 Barbiturates, not elsewhere classified

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y470 Benzodiazepines

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y471 Cloral derivatives

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y472 Paraldehyde

Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)
Y473 Bromine compounds
Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)

Y475 Mixed sedatives and hypnotics, not elsewhere classified

Y478 Other sedatives, hypnotics and antianxiety drugs

Y479 Sedative, hypnotic and antianxiety drug, unspecified

Y480 Inhaled anaesthetics

Y481 Parenteral anaesthetics

Y482 Other and unspecified general anaesthetics

Y483 Local anaesthetics

Y484 Anaesthetic, unspecified

Y485 Therapeutic gases

Y490 Tricyclic and tetracyclic antidepressants

Y491 Monoamine-oxidase-inhibitor antidepressants

Y492 Other and unspecified antidepressants

Y493 Phenothiazine antipsychotics and neuroleptics

Y494 Butyrophenone and thioxanthene neuroleptics

Y495 Other antipsychotics and neuroleptics

Y496 Psychodysleptics [hallucinogens]

Y497 Psychostimulants with abuse potential
Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)

Y498 Other psychotropic drugs, not elsewhere classified

Y499 Psychotropic drug, unspecified

Y500 Analeptics

Y501 Opioid receptor antagonists

Y502 Methylxanthines, not elsewhere classified

Y508 Other central nervous system stimulants

Y509 Central nervous system stimulant, unspecified

Y510 Anticholinesterase agents

Y511 Other parasympathomimetics [cholinergics]

Y512 Ganglionic blocking drugs, not elsewhere classified

Y513 Other parasympatholytics [anticholinergics and antimuscarinics] and spasmolytics, not elsewhere classified

Y514 Predominantly alpha-adrenoreceptor agonists, not elsewhere classified

Y515 Predominantly beta-adrenoreceptor agonists, not elsewhere classified

Y516 Alpha-adrenoreceptor antagonists, not elsewhere classified

Y517 Beta-adrenoreceptor antagonists, not elsewhere classified

Y518 Centrally acting and adrenergic-neuron-blocking agents, not elsewhere classified

Y519 Other and unspecified drugs primarily affecting the autonomic nervous system
Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)

Y520 Cardiac-stimulant glycosides and drugs of similar action

Y521 Calcium-channel blockers

Y522 Other antidysrhythmic drugs, not elsewhere classified

Y523 Coronary vasodilators, not elsewhere classified

Y524 Angiotensin-converting-enzyme inhibitors

Y525 Other antihypertensive drugs, not elsewhere classified

Y526 Antihyperlipidaemic and antiarteriosclerotic drugs

Y527 Peripheral vasodilators

Y528 Antivaricose drugs, including sclerosing agents

Y529 Other and unspecified agents primarily affecting the cardiovascular system

Y530 Histamine H2-receptor antagonists

Y531 Other antacids and anti-gastric-secretion drugs

Y532 Stimulant laxatives

Y533 Saline and osmotic laxatives

Y534 Other laxatives

Y535 Digestants

Y536 Antidiarrhoeal drugs
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>Y537</td>
<td>Emetics</td>
</tr>
<tr>
<td>Y538</td>
<td>Other agents primarily affecting the gastrointestinal system</td>
</tr>
<tr>
<td>Y539</td>
<td>Agent primarily affecting the gastrointestinal system, unspecified</td>
</tr>
<tr>
<td>Y540</td>
<td>Mineralocorticoids</td>
</tr>
<tr>
<td>Y541</td>
<td>Mineralocorticoid antagonists [aldosterone antagonists]</td>
</tr>
<tr>
<td>Y542</td>
<td>Carbonic-anhydrase inhibitors</td>
</tr>
<tr>
<td>Y543</td>
<td>Benzothiadiazine derivatives</td>
</tr>
<tr>
<td>Y544</td>
<td>Loop [high-ceiling] diuretics</td>
</tr>
<tr>
<td>Y545</td>
<td>Other diuretics</td>
</tr>
<tr>
<td>Y546</td>
<td>Electrolytic, caloric and water-balance agents</td>
</tr>
<tr>
<td>Y547</td>
<td>Agents affecting calcification</td>
</tr>
<tr>
<td>Y548</td>
<td>Agents affecting uric acid metabolism</td>
</tr>
<tr>
<td>Y549</td>
<td>Mineral salts, not elsewhere classified</td>
</tr>
<tr>
<td>Y550</td>
<td>Oxytocic drugs</td>
</tr>
<tr>
<td>Y551</td>
<td>Skeletal muscle relaxants [neuromuscular blocking agents]</td>
</tr>
<tr>
<td>Y552</td>
<td>Other and unspecified agents primarily acting on muscles</td>
</tr>
<tr>
<td>Y553</td>
<td>Antitussives</td>
</tr>
</tbody>
</table>
Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)

Y554 Expectorants

Y555 Anti-common-cold drugs

Y556 Antiasthmatics, not elsewhere classified

Y557 Other and unspecified agents primarily acting on the respiratory system

Y560 Local antifungal, anti-infective and anti-inflammatory drugs, not elsewhere classified

Y561 Antipruritics

Y562 Local astringents and local detergents

Y563 Emollients, demulcants and protectants

Y564 Keratolytics, keratoplastics and other hair treatment drugs and preparations

Y565 Ophthalmological drugs and preparations

Y566 Otorhinolaryngological drugs and preparations

Y567 Dental drugs, topically applied

Y568 Other topical agents

Y569 Topical agent, unspecified

Y570 Appetite depressants [anorectics]

Y571 Lipotropic drugs

Y572 Antidotes and chelating agents, not elsewhere classified
Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)

- Y573 Alcohol deterrents
- Y574 Pharmaceutical excipients
- Y575 X-ray contrast media
- Y576 Other diagnostic agents
- Y577 Vitamins, not elsewhere classified
- Y578 Other drugs and medicaments
- Y579 Drug or medicament, unspecified
- Y580 BCG vaccine
- Y581 Typhoid and paratyphoid vaccine
- Y582 Cholera vaccine
- Y583 Plague vaccine
- Y584 Tetanus vaccine
- Y585 Diphtheria vaccine
- Y586 Pertussis vaccine, including combinations with a pertussis component
- Y588 Mixed bacterial vaccines, except combinations with a pertussis component
- Y589 Other and unspecified bacterial vaccines
- Y590 Viral vaccines
Drugs, medicaments and biological substances causing adverse effects in therapeutic use (Y40-Y59)

Y591 Rickettsial vaccines

Y592 Protozoal vaccines

Y593 Immunoglobulin

Y598 Other specified vaccines and biological substances

Y599 Vaccine or biological substance, unspecified
File S2 - Associations between hospital episodes and primary care factors:
incidence rate ratios
Unadjusted and adjusted rate ratios associated with each reference point (Table 1) for each primary care factor are displayed
* Adjusted for practice, patient population age and sex
** Adjusted for patient population age, sex, ethnicity, morbidity score and IMD, GP age, sex and country of qualification, and practice list size, handedness and QOF achievement on the indicators listed
IRR = incidence rate ratio, CI = confidence interval, IMD = index of multiple deprivation, GP = general practitioner, FTE = full-time equivalent, QOF = Quality and Outcomes Framework

<table>
<thead>
<tr>
<th>Reference point</th>
<th>Unadjusted IRR (95 % CI)*</th>
<th>Adjusted IRR (95 % CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient population factors</strong></td>
<td></td>
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<tr>
<td>IMD</td>
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<tr>
<td>10</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>25</td>
<td>1.152 (1.112, 1.194)</td>
<td>1.146 (1.098, 1.197)</td>
</tr>
<tr>
<td>40</td>
<td>1.234 (1.178, 1.292)</td>
<td>1.204 (1.136, 1.277)</td>
</tr>
<tr>
<td>Patient ethnicity (% white)</td>
<td>100 ref</td>
<td>100 ref</td>
</tr>
<tr>
<td>90</td>
<td>0.982 (0.956, 1.008)</td>
<td>0.969 (0.939, 1.000)</td>
</tr>
<tr>
<td>50</td>
<td>1.126 (1.063, 1.193)</td>
<td>1.079 (0.995, 1.171)</td>
</tr>
<tr>
<td>Patient comorbidity score (registrations/1000 patients)</td>
<td>500 ref</td>
<td>500 ref</td>
</tr>
<tr>
<td>500</td>
<td>1.042 (0.917, 1.184)</td>
<td>1.213 (0.944, 1.558)</td>
</tr>
<tr>
<td>750</td>
<td>1.063 (0.910, 1.242)</td>
<td>1.257 (0.983, 1.607)</td>
</tr>
<tr>
<td>GP factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP supply (FTE/1000 patients)</td>
<td>7.5 ref</td>
<td>7.5 ref</td>
</tr>
<tr>
<td>6</td>
<td>0.977 (0.964, 0.991)</td>
<td>0.976 (0.961, 0.990)</td>
</tr>
<tr>
<td>4.5</td>
<td>0.955 (0.929, 0.983)</td>
<td>0.952 (0.923, 0.982)</td>
</tr>
<tr>
<td>Handedness of practice</td>
<td>Multi-handed ref</td>
<td>Single-handed ref</td>
</tr>
<tr>
<td>1.015 (0.954, 1.081)</td>
<td>1.039 (0.942, 1.146)</td>
<td></td>
</tr>
<tr>
<td>GPs ≥ 50 years (%)</td>
<td>0 ref</td>
<td>0 ref</td>
</tr>
<tr>
<td>50</td>
<td>0.946 (0.887, 1.008)</td>
<td>0.969 (0.907, 1.036)</td>
</tr>
<tr>
<td>100</td>
<td>0.956 (0.896, 1.019)</td>
<td>0.978 (0.909, 1.053)</td>
</tr>
<tr>
<td>GPs with non-UK qualifications (%)</td>
<td>0 ref</td>
<td>0 ref</td>
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<tr>
<td>50</td>
<td>0.981 (0.933, 1.031)</td>
<td>0.923 (0.877, 0.972)</td>
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<tr>
<td>100</td>
<td>1.030 (0.976, 1.086)</td>
<td>0.974 (0.913, 1.039)</td>
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<tr>
<td>Female GPs (%)</td>
<td>0 ref</td>
<td>0 ref</td>
</tr>
<tr>
<td>50</td>
<td>1.023 (0.961, 1.090)</td>
<td>1.058 (0.970, 1.155)</td>
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<tr>
<td>100</td>
<td>1.055 (0.968, 1.149)</td>
<td>1.063 (0.970, 1.165)</td>
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<tr>
<td>QOF indicator achievement</td>
<td>Total QOF points (%) ref</td>
<td>ref</td>
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<tr>
<td>100</td>
<td>ref</td>
<td>ref</td>
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<tr>
<td>95</td>
<td>0.992 (0.953, 1.032)</td>
<td>0.947 (0.901, 0.996)</td>
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<tr>
<td>90</td>
<td>1.007 (0.946, 1.072)</td>
<td>0.932 (0.856, 1.014)</td>
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<tr>
<td>PE07 (%)</td>
<td>100 ref</td>
<td>100 ref</td>
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<tr>
<td>80</td>
<td>1.051 (0.983, 1.125)</td>
<td>1.010 (0.936, 1.090)</td>
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<tr>
<td>60</td>
<td>1.078 (1.000, 1.162)</td>
<td>1.004 (0.921, 1.096)</td>
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<tr>
<td>PE08 (%)</td>
<td>100 ref</td>
<td>100 ref</td>
</tr>
<tr>
<td>80</td>
<td>1.059 (0.993, 1.130)</td>
<td>1.030 (0.958, 1.107)</td>
</tr>
<tr>
<td></td>
<td>CHD06 (%)</td>
<td>CHD08 (%)</td>
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<tr>
<td>---</td>
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<td>------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>1.095 (1.011, 1.186)</td>
<td>1.167 (1.033, 1.319)</td>
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<tr>
<td>90</td>
<td>0.992 (0.904, 1.088)</td>
<td>0.958 (0.838, 1.096)</td>
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<tr>
<td>80</td>
<td>1.009 (0.918, 1.108)</td>
<td>1.082 (0.991, 1.181)</td>
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<tr>
<td></td>
<td>ref</td>
<td>ref</td>
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<td>70</td>
<td></td>
<td>1.614 (1.295, 2.012)</td>
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<tr>
<td>40</td>
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<td>0</td>
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**Note:** The numbers in parentheses are confidence intervals.