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Adverse drug reactions, multimorbidity and polypharmacy: A prospective analysis of one month of medical admissions

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ABSTRACT

Objective To ascertain the burden of adverse drug reactions (ADRs), polypharmacy and multimorbidity through a prospective analysis of all medical admissions to a large University teaching hospital over a one-month period.

Design Prospective observational study.

Setting Liverpool University Hospital Foundation NHS Trust, England.

Participants All medical admissions with greater than 24-hour stay over a one-month period.

Main outcome measures Prevalence of admissions due to an ADR and associated mortality. Prevalence and association of multimorbidity and polypharmacy with ADRs. Estimated local financial cost of admissions where ADR was a contributing or main reason for admission with projected costs for NHS in England.

Results There were 218 identified patient admissions with an ADR giving a prevalence of 18.4%. The majority of these (90.4%) were ADRs that directly resulted in or contributed to admission. ADRs thus accounted for 16.5% of total admissions. Those with an ADR were on average taking more medicines (10.5 vs 7.8 $p<0.01$) and had more co-morbidities than those without an ADR (6.1 vs 5.2, $p<0.01$). Drugs most commonly implicated were diuretics, steroid inhalers, anticoagulants & antiplatelets, proton pump inhibitors, chemotherapeutic agents and antihypertensives. 40.4% of ADRs were classified avoidable or possibly avoidable. The mortality rate due to an ADR was 0.34%. The average length of stay for those with an ADR was 6 days. Direct one month cost to the Trust from ADR admissions was £490,716. Extrapolated nationally the projected annual cost to the NHS in England is 2.21bn.

Conclusion The local prevalence of admission and mortality from ADRs are higher than previously reported. Important factors that could be contributing to this include polypharmacy and multimorbidity. ADRs place a significant burden on patients and healthcare services with associated financial implications. Reducing inappropriate polypharmacy should be a major aim for preventing ADRs.

Strengths and limitations of this study:

- Over 1000 medical admissions were individually reviewed by specialists in clinical pharmacology and general internal medicine in this prospective analysis of adverse drug reactions.
- Standardised criteria, as listed in methods, were used to identify and classify ADRs. This improves the objectivity and reproducibility of the analysis.
- Extrapolating the cost analysis nationally based on medical admissions locally may be unreliable due to differences including local population and services.
- This study does not take into account how commonly each medicine that caused an ADR is prescribed in the local community.

INTRODUCTION

Improved living conditions, and better access to and quality of medical care, has led to increased life expectancy and the associated accumulation of Long Term Conditions (LTC) [1]. According to a report by the Academy of Medical Sciences, multimorbidity is a growing issue globally, particularly in more economically developed countries where it is now considered the norm not the exception [2]. Age is the single biggest risk factor for LTCs such as cancer, cardiovascular disease and neurodegeneration in developed countries. An ageing population is therefore at increased risk of polypharmacy [3]. Care for people with multiple LTCs is often stretched across various single-organ specialists leading to siloed specialty prescribing and increasingly complex medication regimens.

Polypharmacy is the concurrent use of multiple medications by an individual. Numerical definitions vary but it is most commonly defined as taking 5 or more regular medications [4]. The Wessex Academic Health Science Network have developed a set of prescribing comparators to better understand both the numerical and risk-related factors involved in the variation of prescribing of multiple medicines [5]. Appropriate polypharmacy can improve health outcomes in multimorbidity, the co-occurrence of two or more long term conditions. In contrast, potentially inappropriate polypharmacy, wherein the risk of harms from individual medicines may outweigh their benefit in the context of the prescription as a whole, is associated with poor adherence and an increased risk of adverse-drug reactions (ADRs) and interactions [6]. ADRs are an important cause of morbidity and mortality, with significant health implications and associated economic burden. Landmark studies in the USA in 1998 [7] and the UK in 2004 [8] found ADRs to be related to 6.7% and 6.5% of hospital admissions, respectively. More recent systematic reviews have reported figures ranging from 3.6% [9] to 15.6% [10]. Potential reasons for variation in findings include the heterogeneity of methodologies and populations studied.

Addressing avoidable ADRs due to inappropriate prescribing is important to reduce the burden on patients and healthcare systems. There are few adult observational studies of admission ADRs in the United Kingdom that are not focused on a specific populations or drug reactions. To our knowledge there are only 3 in the last 20 years [8,11,12]. The aim of this study was to determine the current impact of ADRs on medical admissions, their association with multimorbidity and polypharmacy, and quantify the economic impact on the National Health Service (NHS). The population studied is broadly geographically comparable to that of Pirmohamed et al 2004 [8].

METHODS

Study data was collected for one month in the city centre site of the Liverpool University Hospital Foundation NHS Trust, a large teaching hospital in Merseyside, England. Approval for data collection was obtained through governance processes within the Trust. All patients referred via the medical assessment unit that were admitted for >24 hours were included. These were mostly via the emergency department but also included primary care referrals and admissions from outpatient clinics. Patients admitted via medicine but transferred to other centres for emergency treatment (such as primary coronary intervention) within 24 hours were included, as their expected inpatient stay would be >24 hours. Information including e-notes, community drug prescriptions and investigations were reviewed to determine if an ADR occurred. An ADR was defined using the Edwards and Aronson criteria [13]. This does not include any type of drug overdose or relapse due to noncompliance. Cases were then defined as either the primary cause of admission, contributing factor or a co-incidental finding and assessed against the following criteria:

- Classification of the reaction as per Rawlins and Thompson [14]
- Causality as per the Liverpool causality assessment tool (LCAT) [15]
- Severity as per the adapted Hartwig severity scale (AHSS) [16]
- Interactions as per the drug interaction probability scale (DIPS) [17]
- Avoidability as per the Liverpool ADR avoidability assessment tool (LAAT) [18]

Factors that suggested an ADR include if it was consistent with the known adverse effect profile of the drug as per the British National Formulary [19], if there was a temporal relationship, and if alternate causes were excluded with history and investigation. Community drug prescription were verified and reviewed with patient electronic notes. This data was available for all admitted patients. If it was documented in the notes that a patient was not taking a medicine listed on their prescription this was not included in our analysis.

Identification of ADRs and subsequent assessment of the above criteria was completed by authors RO and LW. Where consensus was not reached it was assessed by third reviewer MP. Of the 258 patient episodes with possible identified ADRs, there was initial agreement on 236 (91%). For the remainder consensus was obtained following joint review with MP.

Patient Level Information and Costing System (PLICS) data reporting healthcare resource group and hospital costs were obtained from the Liverpool University Hospitals NHS Foundation Trust finance office. Total costs were summed for episodes of admitted care resulting from ADRs (a), and for all other admissions (where ADR was a contributory factor, coincidental, or unrelated; (b)). In order to

extrapolate costs, totals for non-elective short and long stay, and regular day or night admissions, for NHS England (c), were obtained for 2018-19 [20]. Nationally projected costs were estimated as (a.c)/(a+b).

STATISTICAL ANALYSIS

Statistical analysis was performed using the SAS software (Version 9.4, SAS Institute, Cary, NC, USA). The results are presented either as means and standard deviations or frequencies and percentages. Associations between patient characteristics and admission type (ADR/Non-ADR) were investigated using univariable and multivariable logistic regression, with associations presented as odds ratios (OR) with 95% confidence intervals. The multivariable model used backwards selection with a probability of exclusion of 0.1. A P value < 0.05 was regarded as statistically significant.

RESULTS

There were 1,187 admissions with 218 patients with an ADR (18.4%). As some of those had multiple ADRs 235 were identified in total.

Characteristics of adverse drug reactions

145 (66.5%) of the ADRs were the primary cause of admission, with 51 (23.4%) contributing to admission, and 22 (10.1%) co-incidental findings that alone would not have required hospital stay. Thus, ADRs directly caused or contributed to 16.6% of all admissions. Using the Liverpool causality assessment tool [15] 45 (20.6%) were graded as definite, 79 (36.2%) as probable, and 94 (43.1%) as possible ADRs. 40 (18.4%) were graded as avoidable and 46 (21.1%) as possibly avoidable using LAAT criteria [18]. 64 (29.4%) of ADRs were possibly or probably cause by a drug-drug interaction as per DIPS[17]. 188 (86.2%) were Type A reactions as defined by Rawlins and Thompson[14] and 30 (13.8%) Type B. 164 (75.2%) of the ADRs were documented as recognised or acted on by the admitting medical team. The main drugs implicated in ADRs are listed in table 1. There were 4 ADRs (1.8%) that directly resulted in death and a further 5 that were implicated or a contributing factor to death (2.3%) (table 2). The mortality rate directly from ADRs, from all admissions, was therefore 0.42%. Median length of stay of patients with an ADR was 6 days.

Comparison of patients with and without adverse drug reactions

Table 3 shows descriptive statistics of patients with and without ADRs. Logistic regression results are presented in Table 4. Patients with ADRs were older than those without (mean age 73.2 (14.5) vs 66.7 (19.2), OR 1.02 (1.01, 1.03)) and were taking more medicines (mean 10.5 (4.6) vs 7.8 (5.1), OR 1.11 (1.07, 1.14)), with polypharmacy present in 91%, compared to 73% in the non-ADR group. They had more comorbidities (mean 6.1 (3.0) vs 5.2 (3.3), OR 1.08 (1.04, 1.13)), although this variable was not included in the multivariable model (possibly due to its correlation with number of medicines). Those with ADRs were more likely to have liver impairment (6.9% vs 2.8%, OR 2.58 (1.35, 4.93)) and renal impairment (11.0% vs 6.8%, OR 1.69 (1.04, 2.78).

HRG costs were available for 214 (98.2%) patients in the ADR group, and 950 (98.0%) patients in the non-ADR group. Mean costs per episode of care were £2,293 (95% CI 1918, 2668) and £2,131 (95% CI 1899, 2364), respectively. The total costs of admissions resulting from ADR were £309,207, representing 12.3% of the costs of the whole cohort over the 1-month sampling frame. Admissions where ADR was a contributory factor cost £138,762 (5.5%); and where ADR was coincidental, the cost was £42,747 (1.7%). The total costs of non-elective short and long stays, and regular day or

night admissions across all NHS trusts and NHS foundation trusts in England was £17.98 bn in 2018-19, of which we estimate £2.21 bn were due to admissions resulting from ADRs.

DISCUSSION

This study found ADRs in 18.4% of hospital admissions. In 16.6% of admissions, it was the primary cause or a contributing cause suggesting ADRs have a significant burden on hospital admissions. This is over twice as high as the 6.5% found in Pirmohamed 2004 [8] which consisted of broadly the same geographical area. Most commonly implicated medicines included diuretics, steroid based inhalers, anticoagulants, proton pump inhibitors, antiplatelets, chemotherapy agents, anti-hypertensives, opiates and antidepressants/antipsychotics (Table 1). It is important to consider this study does not reflect how often each of these medicines are prescribed in the community. Some of the medicines implicated with the highest number of ADRs and deaths may be a reflection of how commonly they are prescribed. Furthermore, the use of these medicines also provides clinical benefits that reduce morbidity, mortality and need for hospital admissions, and this is not taken into account by our data. Direct mortality from ADRs was 0.42% which is also an increase from Pirmohamed 2004 (0.15%) [8] and twice as high as a recent meta-analysis [21].

Approximately, 40% of ADRs were classified as avoidable or possibly avoidable. This is consistent with previous studies which found significant proportions of ADRs that lead to hospital admissions are potentially avoidable [22]. Given this, future efforts should be targeted at reducing these preventable admissions. Key strategies that can mitigate for ADRs include stratifying patients by susceptibility prior to medication initiation using key information such as co-morbidities, concomitant medications and renal and hepatic function. Where available and appropriate, pharmacogenomic testing can also be used to identify those at high risk of an ADR to guide medication choice, or optimal dose. Following initiation, management plans such as appropriate blood test monitoring and scheduled clinical review for ongoing indication can also reduce the risk of an ADR[23]. 29.4% of ADRs were possibly or probably caused by drug-drug interactions as per DIPS[17]. Given this deprescribing, especially in those on a polypharmacy, could play an important role in reducing ADR burden.

Comparison with Pirmohamed 2004

Pirmohamed et al 2004 [8] was a large prospective study of admission ADRs in two Liverpool hospitals, the large university teaching hospital used in this study and a smaller district general hospital. This found an ADR prevalence in hospital admissions of 6.5%, suggesting there has been a significant increase since 2004. Numerous clinical reasons could have influenced this including

changes in population demographics, increased morbidity and prescribing patterns. Some of the increase may be because pharmacovigilance has improved over the last 20 years, and the adverse reaction profile of drugs is more comprehensive. For example, following a large case control study by Ernst et al [24], an increased risk of pneumonia and dose dependant 30-day mortality from steroid based inhalers in COPD patients was added as a side effect to the British National Formulary. Over 10% of the ADRs in this study are attributable to this. Some ADRs were also secondary to newer therapies including chemotherapies and monoclonal antibodies that have been developed since 2004.

In 2004 two of the main causative medicines were NSAIDs (11.8%) and the antiplatelets (aspirin and clopidogrel) (23.8%). In this study these medicines were implicated in 0.85% and 7.4% of the ADRs respectively. Despite the increase in total ADRs from 2004 this would suggest a large proportional reduction. This is likely due to changes in prescribing practice including co-administration of proton pump inhibitors (PPI). However, this has promoted PPIs as a cause of ADRs from very few cases to being responsible for 12.1% of ADRs in this study. The majority of the reactions were only mild transient electrolyte disturbances, with only a single severe associated ADR of Clostridium difficile.

In recent years, concerns of an opiate crisis due to excessive community prescription has occurred in the USA [25]. In this study, opiate medications accounted for 5.1% of ADRs which is similar to the 6.0% found in 2004. This suggests that proportionally there has not been a significant increase in prescription opiate related admissions locally. Of the related 13 events, the majority were non-lethal, with only 2 cases exhibiting respiratory depression but with no permanent harm following reversal.

Changes in prescribing patterns and subsequent ADRs may reflect increasing multimorbidity and polypharmacy. However, as such data was not previously collected this cannot be directly compared. Furthermore, methodological differences may have contributed as this study did not include any data from a district general hospital or surgical admissions. Additionally, screening and data collection was completed by medical doctors and clinical pharmacologists, whereas previously it was completed by a number of healthcare professionals. Thus, differences in clinical and diagnostic experience could also be responsible for some increased identification of ADRs.

Multimorbidity and Polypharmacy

Multimorbidity and polypharmacy were both associated with admission ADR on univariate analysis. Those with an ADR were taking on average 35% more medicines than those without (10.5 v 7.8), which is an established risk factor for ADRs[26]. Despite this polypharmacy must not be conflated with

inappropriate prescribing as some patients, particularly those that are multimorbid, require multiple medicines to optimise their LTCs with associated positive outcomes. This study did not assess the appropriateness of all community prescriptions, but only of those that directly caused an ADR via the avoidability assessment tool.

The mean number of comorbidities for the entire admitted population was 5.4. Although we do not have direct data from 2004 for comparison it is reported that the incidence of multimorbidity has been increasing [2]. The ADR group on average had 17% more co-morbidities than the non ADR group (6.1 vs 5.2), which is a known risk factor [26]. Although total number of co-morbidities is relevant, it does not to give insight into disease severity which may subsequently influence the number of medications a patient is taking. For example, hypertension or type 2 diabetes managed with lifestyle factors would produce less medication burden than more advanced disease. Furthermore, some conditions and their management are known to predispose to prescribing cascades and therefore polypharmacy [26,27]. This may explain why the number of comorbidities was not significant following logistic regression analysis, with only age, number of medications and liver impairment being significant factors.

Cost analysis

ADRs are a significant cost burden on the NHS, and in this study accounted for £1 in every £8 spent on the care of non-elected hospital admissions. Put into perspective, the total cost of admissions related to ADRs over the 1-month study period (£490,716) is comparable with the annual cost of chemotherapy procurement by the hospital in which the study was conducted. When extrapolated nationally, our estimate of £2.21 bn for admissions resulting from ADRs exceeds the costs of all outpatient procedures for NHS England. Previous cost analyses of medication-related harm in England provide annual estimates of £1.9 bn based on an extrapolation from Pirmohamed et al (2004)[28], £529m for potentially avoidable adverse drug reaction-related admissions [29], and £396m for discharged elderly people [30].

Strengths and weaknesses

Key strengths include that data was collected prospectively and notes were reviewed by specialists in clinical pharmacology and general internal medicine. This optimised the reliability of collected data and identification of ADRs. The availability of patient-level cost data, reflecting the actual spend on hospital care, represents another strength over many previous cost analyses.

Using standardised criteria to identify and classify ADRs improves objectivity and reproducibility as evidenced by levels of concordance >90% between reviewers. However, some elements of the

criteria can be subjective and rely on reviewer clinical experience. Furthermore, many of the medical conditions and side effects attributed to an ADR may have occurred regardless of prescription, for example regarding steroid inhalers and the increased risk of pneumonia in COPD patients. A limitation of our study is that we have not concurrently assessed the benefits of taking medicines in individual patients.

Liverpool is ranked as the most deprived major city in England, an established factor in predicting increased morbidity [31]. With the disparity between the most and least deprived areas in England having increased since the 1990's [32], changes in local population may have influenced differences found from 2004 as well as limit the utility of extrapolation of data nationally.

CONCLUSION

This study found ADRs contributed or directly caused 16.6% of all admissions with an associated mortality rate of 0.34%. Factors associated with an ADR on logistic regression included age, number of medications and liver impairment. The data suggests ADRs place a significant and increasing burden on patients and healthcare services with associated financial implications. Using patient-level cost data the projected annual cost of ADR admissions to the NHS in England is £2.21 bn. With 39.4% of these ADRs identified as avoidable or potentially avoidable future efforts should be directed to reduce this burden. Reducing inappropriate polypharmacy should be a major aim for preventing ADRs.

DECLARATIONS

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There were no patient contributors or co-authors in this study.

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Key messages bullet points

- Adverse drug reactions directly caused or contributed to 16.6% of all medical admissions
- Age, number of medications, multimorbidity, liver impairment and renal impairment are important factors associated with ADRs
- The cost of ADRs when extrapolated nationally may be as high as £2.21 bn per annum in England.

Summary boxes

What we already know on this topic

- In 2004 a large prospective study in the UK found adverse drug reactions accounted for 6.5% of hospital admissions
- Polypharmacy and multimorbidity are becoming increasingly prevalent in the UK population.

What this study adds

- 16.6% of admissions directly or contributed by an ADR, a significant increase from 2004.
- The mortality attributable to adverse drug reactions was 0.34%.
- The projected annual financial cost to NHS in England is £2.1 bn
- Key associated factors included age, number of medications, multimorbidity, renal and hepatic impairment.

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Tables

Table 1 – Drugs implicated in patient episodes with adverse drug reactions*

Drug class	No of ADRs (%)	Offending drug	ADR
Diuretics	31 (14.2%)	Furosemide (13), spironolactone (8), bumetanide (6), bendroflumethiazide (2), coamilofruse (1), indapamide (1)	Renal impairment (18), electrolyte derangement (12), postural hypotension (1)
Steroid inhaler	27 (12.4%)	Steroid inhaler (27)	Pneumonia (26), Oral Thrush (1)
Anticoagulants	21 (9.6%)	Warfarin (7), apixaban (5), edoxaban (4), rivaroxaban (4), enoxaparin (1)	Minor bleeding (10), anaemia (4), intracranial haemorrhage (4), Gastrointestinal bleed (3)
Proton pump inhibitor	18 (8.3%)	Lansoprazole (9), omeprazole (6), pantoprazole (3)	Hypomagnesaemia (11), hyponatraemia (6), C.Diff (1)
Antiplatelet	16 (7.4%)	Aspirin (13), clopidogrel (3)	Intracranial haemorrhage (5), Gastrointestinal bleed (4), minor bleeding (4), anaemia
Chemotherapy	16 (7.3%)	Chemotherapy (16)	Neutropenic Sepsis (8), Sepsis (4), Constipation (1), Deranged electrolytes (1), Rash (1), Thrombocytopenia (1)
ACE-inhibitor / angiotensin receptor blocker	14 (6.4%)	Losartan (4), ramipril (4), irbesartan (3), candesartan (1), lisinopril (1), perindopril (1)	Renal impairment (9), postural hypotension (3), hyperkalaemia (1), renal failure (1)
Antidepressants & Antipsychotics	13 (6.0%)	Mirtazapine (2), sertraline (2), sulpride (2), carbemazapine (1), dosulepin (1), notriptyline (1), olanzapine (1), risperidone (1)	Confusion (3), hyponatraemia (3), parkinsonism (3), constipation (1), gastrointestinal bleed (1), prolonged QTc (1)
Opiates	13 (6.0%)	Codeine (5), morhpine sulphate (3), oxycodone (2), tramadol (2), buprenorphine (1)	Constipation (6), confusion (4), respiratory depression (2), hallucinations (1)
Other	49 (22.4%)	Other (49)	Other (49)
*In those with multiple ADRs only the most severe ADR was included in this table, as defined by the adapted Hartwig severity scale [16]. See supplementary material for full list.			

Table 2– Deaths directly related to the adverse reaction (Adapted Hartwig class 7b)

Medication	Number	Cause of death
Chemotherapy	2	Neutropenic sepsis (2)
Aspirin	1	Intracranial haemorrhage
Edoxaban	1	Gastrointestinal bleed

Table 3 – Characteristics of patients with and without adverse drug reactions

	ADR group	Non ADR group	Total
Number of admissions	218	969	1187
Age Mean (s.d.)	73.2 (14.5)	66.7 (19.2)	67.9 (18.6)
Male (%)	106 (48.6%)	455 (47.0%)	561 (47.3%)
Number of medicines Mean (s.d.)	10.5 (4.6)	7.8 (5.1)	8.3 (5.1)
Polypharmacy (%)	199 (91.3%)	706 (72.9%)	905 (76.2%)
Number of co-morbidities Mean (s.d.)	6.1 (3.0)	5.2 (3.3)	5.4 (3.2)
Multimorbid (%)	216 (99.1%)	875 (90.3%)	1091 (91.9%)
Liver impairment * (%)	15 (6.9%)	27 (2.8%)	42 (3.5%)
Renal impairment ** (%)	24 (11.0%)	66 (6.8%)	90 (7.6%)
* Liver impairment defined as Chronic Liver Disease ** Renal impairment defined as Chronic Kidney Disease stage IV or V			

Table 4: Logistic regression analysis of patients with and without adverse drug reactions

	Univariable odds ratio (95% CI)	p-value (Wald chi-square)	Multivariable odds ratio (95% CI)	p-value (Wald chi-square)
Age	1.02 (1.01, 1.03)	<0.001	1.02 (1.01, 1.03)	<0.001
Sex (Male)	1.07 (0.80, 1.44)	0.659		
Number of medicines	1.11 (1.07, 1.14)	<0.001	1.10 (1.07, 1.13)	<0.001
Number of comorbidities	1.08 (1.04, 1.13)	<0.001		
Liver impairment (CLD)	2.58 (1.35, 4.93)	0.004	3.23 (1.63, 6.40)	<0.001
Renal impairment (CKD stage 4 or 5)	1.69 (1.04, 2.78)	0.036		

Supplementary material - Full list of Adverse reactions by drug class

Drug Class	Number of associated ADRs	Medications implicated	Adverse reaction
Diuretics	31	Furosemide (13), Spironolactone (8), Bumetanide (6), Bendroflumethiazide (2), Coamilofruse (1), Indapamide (1)	Renal impairment (18), Electrolyte derrangement (12), Postural hypotension (1)
Steriod inhailer	27	Steroid inhailer (27)	CAP (26), Oral Thrush (1)
Anticoagulants	21	Warfarin (7), Apixaban (5), Edoxaban (4), Rivaroxaban (4), Enoxaparin (1)	Minor bleeding (10), Anaemia (4), Intracranial haemmhorage (4), GI bleed (3)
PPI	18	Lansoprazole (9), Omeprazole (6), Pantoprazole (3)	Hypomagnasaemia (11), Hyponatraemia (6), C.Diff (1)
Antiplatlets	16	Aspirin (13), Clopidogrel (3)	Intracranial haemoorhage (5), GI bleed (4), Minor bleeding (4), Anaemia
Chemotherapy	16	Chemotherapy (16)	Neutropenic Sepsis (8), Sepsis (4), Constipation (1), Derranged electrolytes (1), Rash (1), Thromocytopenia (1)
ACE-i/ARB	14	Losartan (4), Ramipril (4), Irbesartan (3), Candesartan (1), Lisinopril (1), Perindopril (1)	Renal impairment (9), Postural hypotension (3), Hyperkalaemia (1), Renal failure (1)
Antidepressants & antipsychotics	13	Mirtazapine (2), Sertraline (2), Sulpride (2), Carbemazapine (1), Dosulepin (1), Notriptyline (1), Olanzapine (1), Risperidone (1)	Confusion (3), Hyponatraemia (3), Parkinsonism (3), Constipation (1), GI bleed (1), Prolonged QTc (1)
Opiates	13	Codeine (5), Morhpine Sulphate (3), Oxycodone (2), Tramadol (2), Buprenorphine (1)	Constipation (6), Confusion (4), Respiratory Depression (2), Hallucinations (1)
B-blockers	9	Bisoprolol (6), Atenolol (1), Nebivolol (1), Propanolol (1)	Bradycardia (5), Postural hypotension (4)
Insulin	7	Insulin (7)	Hypoglycaemia (4), Hypoglycaemic seizures (2)
CCB	6	Amlodipine (4), Ivabradine (1), Diltiazem (1)	Postural hypotension (5), Prolonged QTc (1)
Bladder anticholenergics	6	Solifenacin (4), Tolterodine (1), Tropsium (1)	Confusion (4), Constipation (2)
Immunosuprresants	5	MMF (3), Tacrolimus (2)	Sepsis (5)
Antimicrobials	4	Penicillin (2), Aciclovir (1), Azithromicin (1)	Angioedema (1), Rash (1), Renal impairment (1), Prolonged QTc (1)
Oral anti diabetics	4	Gliclazide (2), Empaglaflozin (1), Pioglitazone (1)	Hypoglycaemia (2), Heart Failure (1), Urinary Tract infection (1)

Monoclonals	3	Afatanib (1), Penbrolizumab (1), Ruxolitib (1)	Liver toxicity (1), Pneomonitis (1), Sepsis (1)
Statins	2	Atorvastatin (1), Simvastatin (1)	Myopathy (2)
Levodopa	2	Co-beneldopa (1), Co-careldopa (1)	Postural Hypotension (2)
PTH Analogues	2	Alfacalcidol (1), Calcitriol (1)	Hypercalcaemia (2)
NSAIDs	2	Naproxen (2)	ACS (1), GI Bleed (1)
Benzodiazepines	2	Lorazepam (1), Tempazepam (1)	Confusion (2)
Baclofen	1	Baclofen (1)	Consitpation (1)
Amitriptyline	1	Amitriptyline (1)	Confusion (1)
Leviteracitem	1	Leviterecitem (1)	Renal impairment (1)
Doxazocin	1	Doxazocin (1)	Postural hypotension (1)
Nefopam	1	Nefopam (1)	Delirium (1)
Quinnine	1	Quinnine (1)	Prolonged QTc (1)
Lithium	1	Lithium (1)	Lithium Toxicity (1)
Laxatives	1	Laxatives (1)	Diahrroea (1)
Bisphophanates	1	Alendronic Acid (1)	Erosive Gastritis (1)
Thyroxine	1	Levothyroxine (1)	Tachyarrythmia (1)
Zopiclone	1	Zopiclone (1)	Confusion (1)
Phosphodiesterase inhibitor	1	Uniphyllin (1)	Nausea (1)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	4
		(*e*) Describe any sensitivity analyses	n/a

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	16
		(b) Indicate number of participants with missing data for each variable of interest	4
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*n/a*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*n/a*
		Cross-sectional study—Report numbers of outcome events or summary measures	*16*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16
		(*b*) Report category boundaries when continuous variables were categorized	16
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Additional

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Adverse drug reactions, multimorbidity and polypharmacy: A prospective analysis of one month of medical admissions

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ABSTRACT

Objective To ascertain the burden and associated cost of adverse drug reactions (ADRs), polypharmacy and multimorbidity through a prospective analysis of all medical admissions to a large University teaching hospital over a one-month period.

Design Prospective observational study.

Setting Liverpool University Hospital Foundation NHS Trust, England.

Participants All medical admissions with greater than 24-hour stay over a one-month period.

Main outcome measures Prevalence of admissions due to an ADR and associated mortality. Prevalence and association of multimorbidity and polypharmacy with ADRs. Estimated local financial cost of admissions where ADR was a contributing or main reason for admission with projected costs for NHS in England.

Results There were 218 identified patient admissions with an ADR giving a prevalence of 18.4%. The majority of these (90.4%) were ADRs that directly resulted in or contributed to admission. ADRs thus accounted for 16.5% of total admissions. Those with an ADR were on average taking more medicines (10.5 vs 7.8 $p<0.01$) and had more co-morbidities than those without an ADR (6.1 vs 5.2, $p<0.01$). Drugs most commonly implicated were diuretics, steroid inhalers, anticoagulants & antiplatelets, proton pump inhibitors, chemotherapeutic agents and antihypertensives. 40.4% of ADRs were classified avoidable or possibly avoidable. The mortality rate due to an ADR was 0.34%. The average length of stay for those with an ADR was 6 days. Direct one month cost to the Trust from ADR admissions was £490,716. Extrapolated nationally the projected annual cost to the NHS in England is 2.21 billion.

Conclusion The local prevalence of admission and mortality from ADRs are higher than previously reported. Important factors that could be contributing to this include polypharmacy and multimorbidity. ADRs place a significant burden on patients and healthcare services with associated financial implications. Reducing inappropriate polypharmacy should be a major aim for preventing ADRs.

Strengths and limitations of this study:

- Over 1000 medical admissions were individually reviewed by specialists in clinical pharmacology and general internal medicine in this prospective analysis of adverse drug reactions.
- Standardised criteria, as listed in methods, were used to identify and classify ADRs. This improves the objectivity and reproducibility of the analysis.
- Extrapolating the cost analysis nationally based on medical admissions locally may be unreliable due to differences including local population and services.
- This study does not take into account how commonly each medicine that caused an ADR is prescribed in the local community.

INTRODUCTION

Improved living conditions, and better access to and quality of medical care, has led to increased life expectancy and the associated accumulation of Long Term Conditions (LTC) [1]. According to a report by the Academy of Medical Sciences, multimorbidity is a growing issue globally, particularly in more economically developed countries where it is now considered the norm not the exception [2]. Age is the single biggest risk factor for LTCs such as cancer, cardiovascular disease and neurodegeneration in developed countries. An ageing population is therefore at increased risk of polypharmacy [3]. Care for people with multiple LTCs is often stretched across various single-organ specialists leading to siloed specialty prescribing and increasingly complex medication regimens.

Polypharmacy is the concurrent use of multiple medications by an individual. Numerical definitions vary but it is most commonly defined as taking 5 or more regular medications [4]. The Wessex Academic Health Science Network have developed a set of prescribing comparators to better understand both the numerical and risk-related factors involved in the variation of prescribing of multiple medicines [5]. Appropriate polypharmacy can improve health outcomes in multimorbidity, the co-occurrence of two or more long term conditions. In contrast, potentially inappropriate polypharmacy, wherein the risk of harms from individual medicines may outweigh their benefit in the context of the prescription as a whole, is associated with poor adherence and an increased risk of adverse-drug reactions (ADRs) and interactions [6]. ADRs are an important cause of morbidity and mortality, with significant health implications and associated economic burden. Landmark studies in the USA in 1998 [7] and the UK in 2004 [8] found ADRs to be related to 6.7% and 6.5% of hospital admissions, respectively. More recent systematic reviews have reported figures ranging from 3.6% [9] to 15.6% [10]. Potential reasons for variation in findings include the heterogeneity of methodologies and populations studied.

Addressing avoidable ADRs due to inappropriate prescribing is important to reduce the burden on patients and healthcare systems. There are few adult observational studies of admission ADRs in the United Kingdom that are not focused on a specific populations or drug reactions. To our knowledge there are only 3 in the last 20 years [8,11,12]. In 2016, it was estimated that £1.3-3 billion could be saved in the NHS budget through reducing inappropriate and inefficient medicines usage[13].

The aim of this study was to determine the current impact of ADRs on medical admissions, their association with multimorbidity and polypharmacy, and quantify the economic impact on the National Health Service (NHS). The population studied is broadly geographically comparable to that of Pirmohamed et al 2004 [8].

METHODS

Study data was collected for one month in the city centre site of the Liverpool University Hospital Foundation NHS Trust, a large teaching hospital in Merseyside, England. Approval for data collection was obtained through governance processes within the Trust. All patients referred via the medical assessment unit that were admitted for >24 hours were included. These were mostly via the emergency department but also included primary care referrals and admissions from outpatient clinics. Patients admitted via medicine but transferred to other centres for emergency treatment (such as primary coronary intervention) within 24 hours were included, as their expected inpatient stay would be >24 hours. Information including e-notes, community drug prescriptions and investigations were reviewed to determine if an ADR occurred. An ADR was defined using the Edwards and Aronson criteria [14]. This does not include any type of drug overdose or relapse due to noncompliance. Cases were then defined as either the primary cause of admission, contributing factor or a co-incidental finding and assessed against the following criteria:

- Classification of the reaction as per Rawlins and Thompson [15]
- Causality as per the Liverpool causality assessment tool (LCAT) [16]
- Severity as per the adapted Hartwig severity scale (AHSS) [17]
- Interactions as per the drug interaction probability scale (DIPS) [18]
- Avoidability as per the Liverpool ADR avoidability assessment tool (LAAT) [19]

Factors that suggested an ADR include if it was consistent with the known adverse effect profile of the drug as per the British National Formulary [20], if there was a temporal relationship, and if alternate causes were excluded with history and investigation. Community drug prescription were verified and reviewed with patient electronic notes. This data was available for all admitted patients. If it was documented in the notes that a patient was not taking a medicine listed on their prescription this was not included in our analysis.

Identification of ADRs and subsequent assessment of the above criteria was completed by authors RO and LW. Where consensus was not reached it was assessed by third reviewer MP. Of the 258 patient episodes with possible identified ADRs, there was initial agreement on 236 (91%). For the remainder consensus was obtained following joint review with MP.

Patient Level Information and Costing System (PLICS) data reporting healthcare resource group and hospital costs were obtained from the Liverpool University Hospitals NHS Foundation Trust finance office. Total costs were summed for episodes of admitted care resulting from ADRs (a), and for all other admissions (where ADR was a contributory factor, coincidental, or unrelated; (b)). In order to

extrapolate costs, totals for non-elective short and long stay, and regular day or night admissions, for NHS England (c), were obtained for 2018-19 [21]. Nationally projected costs were estimated as (a.c)/(a+b).

Ethics Approval

Approval for this study was granted by Liverpool University Hospital Foundation NHS Trust clinical audit and service evaluation department (Project number 7580).

Patient and public involvement

The research question was developed due to the impact ADRs have on patients by causing admissions to hospital. There were no patient contributors or co-authors in this study.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SAS software (Version 9.4, SAS Institute, Cary, NC, USA). The results are presented either as means and standard deviations or frequencies and percentages. Associations between patient characteristics and admission type (ADR/Non-ADR) were investigated using univariable and multivariable logistic regression, with associations presented as odds ratios (OR) with 95% confidence intervals. The multivariable model used backwards selection with a probability of exclusion of 0.1. A P value < 0.05 was regarded as statistically significant.

RESULTS

There were 1,187 admissions with 218 patients with an ADR (18.4%). As some of those had multiple ADRs 235 were identified in total.

Characteristics of adverse drug reactions

145 (66.5%) of the ADRs were the primary cause of admission, with 51 (23.4%) contributing to admission, and 22 (10.1%) co-incidental findings that alone would not have required hospital stay. Thus, ADRs directly caused or contributed to 16.6% of all admissions. Using the Liverpool causality assessment tool [16] 45 (20.6%) were graded as definite, 79 (36.2%) as probable, and 94 (43.1%) as possible ADRs. 40 (18.4%) were graded as avoidable and 46 (21.1%) as possibly avoidable using LAAT criteria [19]. 64 (29.4%) of ADRs were possibly or probably cause by a drug-drug interaction as per DIPS[18]. 188 (86.2%) were Type A reactions as defined by Rawlins and Thompson[15] and 30 (13.8%) Type B. 164 (75.2%) of the ADRs were documented as recognised or acted on by the admitting medical team. The main drugs implicated in ADRs are listed in table 1. There were 4 ADRs (1.8%) that directly resulted in death and a further 5 that were implicated or a contributing factor to death (2.3%) (table 2). The mortality rate directly from ADRs, from all admissions, was therefore 0.42%. Median length of stay of patients with an ADR was 6 days.

Comparison of patients with and without adverse drug reactions

Table 3 shows descriptive statistics of patients with and without ADRs. In the patients with ADRs, as would be expected, liver and renal impairment were more prevalent compared to patients without ADRs (6.8% vs 2.8%, p 0.004).

Logistic regression results are presented in Table 4. Patients with ADRs were older than those without (mean age 73.2 (14.5) vs 66.7 (19.2), OR 1.02 (1.01, 1.03)) and were taking more medicines (mean 10.5 (4.6) vs 7.8 (5.1), OR 1.11 (1.07, 1.14)), with polypharmacy present in 91%, compared to 73% in the non-ADR group. They had more comorbidities (mean 6.1 (3.0) vs 5.2 (3.3), OR 1.08 (1.04, 1.13)), although this variable was not included in the multivariable model (possibly due to its correlation with number of medicines). Those with ADRs were more likely to have liver impairment (6.9% vs 2.8%, OR 2.58 (1.35, 4.93)) and renal impairment (11.0% vs 6.8%, OR 1.69 (1.04, 2.78).

Healthcare Resource Group (HRG) costs were available for 214 (98.2%) patients in the ADR group, and 950 (98.0%) patients in the non-ADR group. Mean costs per episode of care were £2,293 (95% CI 1918, 2668) and £2,131 (95% CI 1899, 2364), respectively. The total costs of admissions resulting from ADR were £309,207, representing 12.3% of the costs of the whole cohort over the 1-month sampling frame. Admissions where ADR was a contributory factor cost £138,762 (5.5%); and where

ADR was coincidental, the cost was £42,747 (1.7%). The total costs of non-elective short and long stays, and regular day or night admissions across all NHS trusts and NHS foundation trusts in England was £17.98 billion in 2018-19, of which we estimate £2.21 billion were due to admissions resulting from ADRs.

DISCUSSION

This study found ADRs in 18.4% of hospital admissions. In 16.6% of admissions, it was the primary cause or a contributing cause suggesting ADRs have a significant burden on hospital admissions. This is over twice as high as the 6.5% found in Pirmohamed 2004 [8] which consisted of broadly the same geographical area. Most commonly implicated medicines included diuretics, steroid based inhalers, anticoagulants, proton pump inhibitors, antiplatelets, chemotherapy agents, anti-hypertensives, opiates and antidepressants/antipsychotics (Table 1). It is important to consider this study does not reflect how often each of these medicines are prescribed in the community. Some of the medicines implicated with the highest number of ADRs and deaths may be a reflection of how commonly they are prescribed. Furthermore, the use of these medicines also provides clinical benefits that reduce morbidity, mortality and need for hospital admissions, and this is not taken into account by our data. Direct mortality from ADRs was 0.42% which is also an increase from Pirmohamed 2004 (0.15%) [8] and twice as high as a recent meta-analysis [22].

Approximately, 40% of ADRs were classified as avoidable or possibly avoidable. This is consistent with previous studies which found significant proportions of ADRs that lead to hospital admissions are potentially avoidable [23]. Given this, future efforts should be targeted at reducing these preventable admissions. Key strategies that can mitigate for ADRs include stratifying patients by susceptibility prior to medication initiation using key information such as co-morbidities, concomitant medications and renal and hepatic function. Where available and appropriate, pharmacogenomic testing can also be used to identify those at high risk of an ADR to guide medication choice, or optimal dose. Following initiation, management plans such as appropriate blood test monitoring and scheduled clinical review for ongoing indication can also reduce the risk of an ADR[24]. 29.4% of ADRs were possibly or probably caused by drug-drug interactions as per DIPS[18]. Deprescribing, defined as the process of dose-reduction or stopping of medicines by a healthcare professional, has been proposed as an important tool to reduce the burden of ADRs. The optimal use of medicines should include the entire prescribing spectrum including starting, dose-adjustment and stopping at the point at which harm outweighs benefit.

Comparison with Pirmohamed 2004

Pirmohamed et al 2004 [8] was a large prospective study of admission ADRs in two Liverpool hospitals, the large university teaching hospital used in this study and a smaller district general hospital. This found an ADR prevalence in hospital admissions of 6.5%, suggesting there has been a significant increase since 2004. Numerous clinical reasons could have influenced this including changes in population demographics, increased morbidity and prescribing patterns. Some of the increase may be because pharmacovigilance has improved over the last 20 years, and the adverse reaction profile of drugs is more comprehensive. For example, following a large case control study by Ernst et al [25], an increased risk of pneumonia and dose dependant 30-day mortality from steroid based inhalers in COPD patients was added as a side effect to the British National Formulary. Over 10% of the ADRs in this study are attributable to this. Some ADRs were also secondary to newer therapies including chemotherapies and monoclonal antibodies that have been developed since 2004.

In 2004 two of the main causative medicines were NSAIDs (11.8%) and the antiplatelets (aspirin and clopidogrel) (23.8%). However, in this more recent study these medicines were implicated in only 0.85% and 7.4% of the ADRs respectively. Despite the increase in total ADRs from 2004 this would suggest a large proportional reduction. This could be due to greater awareness of these ADRs in older people leading to enhanced pharmacovigilance in prescribers along with changes in prescribing practice including co-administration of proton pump inhibitors (PPI). However, this change has promoted PPIs as a cause of ADRs from very few cases to being responsible for 12.1% of ADRs in this study. The majority of the reactions were only mild transient electrolyte disturbances, with only a single severe associated ADR of *Clostridium difficile*. In the case of anti-platelets, two factors are likely to have to contributed to this change: (a) there has been an active programme of reduction in their use for primary prevention of cardiovascular disease; and (b) changes in atrial fibrillation guidelines has led a greater use of anticoagulants rather than antiplatelets.

In recent years, concerns of an opiate crisis due to excessive community prescription has occurred in the USA [26]. In this study, opiate medications accounted for 5.1% of ADRs which is similar to the 6.0% found in 2004. This suggests that proportionally there has not been a significant increase in prescription opiate related admissions locally. Of the related 13 events, the majority were non-lethal, with only 2 cases exhibiting respiratory depression but with no permanent harm following reversal.

Changes in prescribing patterns and subsequent ADRs may reflect increasing multimorbidity and polypharmacy. However, as such data was not previously collected this cannot be directly compared. Furthermore, methodological differences may have contributed as this study did not include any

data from a district general hospital or surgical admissions. Additionally, screening and data collection was completed by medical doctors and clinical pharmacologists, whereas previously it was completed by a number of healthcare professionals. Thus, differences in clinical and diagnostic experience could also be responsible for some increased identification of ADRs.

Multimorbidity and Polypharmacy

Multimorbidity and polypharmacy were both associated with admission ADR on univariate analysis. Those with an ADR were taking on average 35% more medicines than those without (10.5 v 7.8, p <0.001), which is an established risk factor for ADRs[27]. Despite this polypharmacy must not be conflated with inappropriate prescribing as some patients, particularly those that are multimorbid, require multiple medicines to optimise their LTCs with associated positive outcomes. This study did not assess the appropriateness of all community prescriptions, but only of those that directly caused an ADR via the avoidability assessment tool.

The mean number of comorbidities for the entire admitted population was 5.4. Although we do not have direct data from 2004 for comparison it is reported that the incidence of multimorbidity has been increasing [2]. The ADR group on average had 17% more co-morbidities than the non-ADR group (6.1 vs 5.2, p<0.001), which is a known risk factor [27]. Although total number of co-morbidities is relevant, it does not to give insight into disease severity which may subsequently influence the number of medications a patient is taking. For example, hypertension or type 2 diabetes managed with lifestyle factors would produce less medication burden than more advanced disease. Furthermore, some conditions and their management are known to predispose to prescribing cascades and therefore polypharmacy [27,28]. This may explain why the number of comorbidities was not significant following logistic regression analysis, with only age, number of medications and liver impairment being significant factors.

Cost analysis

ADRs are a significant cost burden on the NHS, and in this study accounted for £1 in every £8 spent on the care of non-elected hospital admissions. Put into perspective, the total cost of admissions related to ADRs over the 1-month study period (£490,716) is comparable with the annual cost of chemotherapy procurement by the hospital in which the study was conducted. When extrapolated nationally, our estimate of £2.21 billion for admissions resulting from ADRs exceeds the costs of all outpatient procedures for NHS England. Previous cost analyses of medication-related harm in England provide annual estimates of £1.9 billion based on an extrapolation from Pirmohamed et al

(2004)[29], £529m for potentially avoidable adverse drug reaction-related admissions [30], and £396m for discharged elderly people [31].

Strengths and weaknesses

Key strengths include that data was collected prospectively and notes were reviewed by specialists in clinical pharmacology and general internal medicine. This optimised the reliability of collected data and identification of ADRs. The availability of patient-level cost data, reflecting the actual spend on hospital care, represents another strength over many previous cost analyses.

Using standardised criteria to identify and classify ADRs improves objectivity and reproducibility as evidenced by levels of concordance >90% between reviewers. However, some elements of the criteria can be subjective and rely on reviewer clinical experience. Furthermore, many of the medical conditions and side effects attributed to an ADR may have occurred regardless of prescription, for example regarding steroid inhalers and the increased risk of pneumonia in COPD patients. A limitation of our study is that we have not concurrently assessed the benefits of taking medicines in individual patients.

It must be emphasised that causality assessment is a time-consuming process requiring clinical insight and therefore it is challenging to do this in time-limited real-world clinical practice. In the future, efforts to enhance the usability of electronic health care records, utilising time-saving approaches such as artificial intelligence and machine learning, could make medicines optimisation more efficient.

Liverpool is ranked as the most deprived major city in England, an established factor in predicting increased morbidity [32]. With the disparity between the most and least deprived areas in England having increased since the 1990's [33], changes in local population may have influenced differences found from 2004 as well as limit the utility of extrapolation of data nationally. In addition, generalisability of this data to more ethnically diverse populations is limited as Liverpool is 88% white[34].

CONCLUSION

This study found ADRs contributed or directly caused 16.6% of all admissions with an associated mortality rate of 0.34%. Factors associated with an ADR on logistic regression included age, number of medications and liver impairment. The data suggests ADRs place a significant and increasing burden on patients and healthcare services with associated financial implications. Using patient-level cost data the projected annual cost of ADR admissions to the NHS in England is £2.21 billon. With

39.4% of these ADRs identified as avoidable or potentially avoidable future efforts should be directed to reduce this burden. Reducing inappropriate polypharmacy should be a major aim for preventing ADRs.

Contributors statement

Dr Rostam Osanlou undertook data collection, statistical analysis and wrote the initial draft of the paper. Dr Lauren Walker was involved in data collection, second reviewer and paper write up. Professor Dyfrig Hughes undertook the cost analysis in this study and contributed to write up. Dr Girvan Burnside undertook statistical analysis and contributed to paper write up. Professor Sir Munir Pirmohamed came up with the idea, and was involved in assessing clinical cases and in reviewing the initial drafts and final draft of the paper.

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Patient and public involvement

The research question was developed due to the impact ADRs have on patients by causing admissions to hospital. There were no patient contributors or co-authors in this study.

Data sharing statement

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd ("BMJ"), and its Licencees to permit this article (if accepted) to be published in The BMJ's editions and any other BMJ products and to exploit all subsidiary rights, as set out in licence.

Key messages bullet points

- Adverse drug reactions directly caused or contributed to 16.6% of all medical admissions

- Age, number of medications, multimorbidity, liver impairment and renal impairment are important factors associated with ADRs
- The cost of ADRs when extrapolated nationally may be as high as £2.21 billion per annum in England.

Summary boxes

What we already know on this topic

- In 2004 a large prospective study in the UK found adverse drug reactions accounted for 6.5% of hospital admissions
- Polypharmacy and multimorbidity are becoming increasingly prevalent in the UK population.

What this study adds

- 16.6% of admissions directly or contributed by an ADR, a significant increase from 2004.
- The mortality attributable to adverse drug reactions was 0.34%.
- The projected annual financial cost to NHS in England is £2.1 billion
- Key associated factors included age, number of medications, multimorbidity, renal and hepatic impairment.

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Tables

Table 1 – Drugs implicated in patient episodes with adverse drug reactions*

Drug class	No of ADRs (%)	Offending drug	ADR
Diuretics	31 (14.2%)	Furosemide (13), pironolactone (8), bumetanide (6), bendroflumethiazide (2), coamilofruse (1), indapamide (1)	Renal impairment (18), electrolyte derangement (12), postural hypotension (1)
Steroid inhaler	27 (12.4%)	Steroid inhaler (27)	Pneumonia (26), Oral Thrush (1)
Anticoagulants	21 (9.6%)	Warfarin (7), apixaban (5), edoxaban (4), rivaroxaban (4), enoxaparin (1)	Minor bleeding (10), anaemia (4), intracranial haemorrhage (4), Gastrointestinal bleed (3)
Proton pump inhibitor	18 (8.3%)	Lansoprazole (9), omeprazole (6), pantoprazole (3)	Hypomagnesaemia (11), hyponatraemia (6), C.Diff (1)
Antiplatelet	16 (7.4%)	Aspirin (13), clopidogrel (3)	Intracranial haemorrhage (5), Gastrointestinal bleed (4), minor bleeding (4), anaemia
Chemotherapy	16 (7.3%)	Chemotherapy (16)	Neutropenic Sepsis (8), Sepsis (4), Constipation (1), Deranged electrolytes (1), Rash (1), Thrombocytopenia (1)
ACE[(1)]-inhibitor / angiotensin receptor blocker	14 (6.4%)	Losartan (4), ramipril (4), irbesartan (3), candesartan (1), lisinopril (1), perindopril (1)	Renal impairment (9), postural hypotension (3), hyperkalaemia (1), renal failure (1)
Antidepressants & Antipsychotics	13 (6.0%)	Mirtazapine (2), sertraline (2), sulpride (2), carbemazapine (1), dosulepin (1), notriptyline (1), olanzapine (1), risperidone (1)	Confusion (3), hyponatraemia (3), parkinsonism (3), constipation (1), gastrointestinal bleed (1), prolonged QTc [(2)](1)
Opiates	13 (6.0%)	Codeine (5), morhpine sulphate (3), oxycodone (2), tramadol (2), buprenorphine (1)	Constipation (6), confusion (4), respiratory depression (2), hallucinations (1)
Other	49 (22.4%)	Other (49)	Other (49)

[(1)] Angiotensin converting enzyme [(2)] Corrected QT interval
*In those with multiple ADRs only the most severe ADR was included in this table, as defined by the adapted Hartwig severity scale [(16).] See supplementary material for full list.

Table 2– Deaths directly related to the adverse reaction (Adapted Hartwig class 7b)

Medication	Number	Cause of death
Chemotherapy	2	Neutropenic sepsis (2)
Aspirin	1	Intracranial haemorrhage
Edoxaban	1	Gastrointestinal bleed

Table 3 – Characteristics of patients with and without adverse drug reactions

	ADR [(1)] group	Non ADR group	Total
Number of admissions	218	969	1187
Age Mean (s.d.)	73.2 (14.5)	66.7 (19.2)	67.9 (18.6)
Male (%)	106 (48.6%)	455 (47.0%)	561 (47.3%)
Number of medicines Mean (s.d.)	10.5 (4.6)	7.8 (5.1)	8.3 (5.1)
Polypharmacy (%)	199 (91.3%)	706 (72.9%)	905 (76.2%)
Number of co-morbidities Mean (s.d.)	6.1 (3.0)	5.2 (3.3)	5.4 (3.2)
Multimorbid (%)	99.1%	90.3%	91.9%
Liver impairment * (%)	6.9%	2.8%	3.5%
Renal impairment **(%)	11.0%	6.8%	7.6%

[(1)] Adverse drug reation
* Liver impairment defined as Chronic Liver Disease
** Renal impairment defined as Chronic Kidney Disease stage IV or V

Table 4: Logistic regression analysis of patients with and without adverse drug reactions

	Univariable odds ratio (95% CI)	p-value (Wald chi-square)	Multivariable odds ratio (95% CI)	p-value (Wald chi-square)
Age	1.02 (1.01, 1.03)	<0.001	1.02 (1.01, 1.03)	<0.001
Sex (Male)	1.07 (0.80, 1.44)	0.659		
Number of medicines	1.11 (1.07, 1.14)	<0.001	1.10 (1.07, 1.13)	<0.001
Number of comorbidities	1.08 (1.04, 1.13)	<0.001		
Liver impairment (CLD)	2.58 (1.35, 4.93)	0.004	3.23 (1.63, 6.40)	<0.001
Renal impairment (CKD stage 4 or 5)	1.69 (1.04, 2.78)	0.036		

Supplementary material - Full list of Adverse reactions by drug class

Drug Class	Number of associated ADRs	Medications implicated	Adverse reaction
Diuretics	31	Furosemide (13), Spironolactone (8), Bumetanide (6), Bendroflumethiazide (2), Coamilofruse (1), Indapamide (1)	Renal impairment (18), Electrolyte derrangement (12), Postural hypotension (1)
Steroid inhailer	27	Steroid inhailer (27)	CAP (26), Oral Thrush (1)
Anticoagulants	21	Warfarin (7), Apixaban (5), Edoxaban (4), Rivaroxaban (4), Enoxaparin (1)	Minor bleeding (10), Anaemia (4), Intracranial haemmhorage (4), GI bleed (3)
Proton Pump Inhibitor	18	Lansoprazole (9), Omeprazole (6), Pantoprazole (3)	Hypomagnasaemia (11), Hyponatraemia (6), C.Diff (1)
Antiplatlets	16	Aspirin (13), Clopidogrel (3)	Intracranial haemoorhage (5), GI bleed (4), Minor bleeding (4), Anaemia
Chemotherapy	16	Chemotherapy (16)	Neutropenic Sepsis (8), Sepsis (4), Constipation (1), Derranged electrolytes (1), Rash (1), Thromocytopenia (1)
ACE-I [(1)] /ARB [(2)]	14	Losartan (4), Ramipril (4), Irbesartan (3), Candesartan (1), Lisinopril (1), Perindopril (1)	Renal impairment (9), Postural hypotension (3), Hyperkalaemia (1), Renal failure (1)
Antidepressants & antipsychotics	13	Mirtazapine (2), Sertraline (2), Sulpride (2), Carbemazapine (1), Dosulepin (1), Notriptyline (1), Olanzapine (1), Risperidone (1)	Confusion (3), Hyponatraemia (3), Parkinsonism (3), Constipation (1), GI bleed (1), Prolonged QTc (1)
Opiates	13	Codeine (5), Morhpine Sulphate (3), Oxycodone (2), Tramadol (2), Buprenorphine (1)	Constipation (6), Confusion (4), Respiratory Depression (2), Hallucinations (1)
Beta adrenoceptor blockers	9	Bisoprolol (6), Atenolol (1), Nebivolol (1), Propanolol (1)	Bradycardia (5), Postural hypotension (4)
Insulin	7	Insulin (7)	Hypoglycaemia (4), Hypoglycaemic seizures (2)
Calcium Channel Blocker	6	Amlodipine (4), Ivabradine (1), Diltiazem (1)	Postural hypotension (5), Prolonged QTc (1)
Bladder anticholenergics	6	Solifenacin (4), Tolterodine (1), Tropsium (1)	Confusion (4), Constipation (2)
Immunosuprresants	5	MMF (3), Tacrolimus (2)	Sepsis (5)
Antimicrobials	4	Penicillin (2), Aciclovir (1), Azithromicin (1)	Angioedema (1), Rash (1), Renal impairment (1), Prolonged QTc (1)

Oral anti diabetics	4	Gliclazide (2), Empaglaflozin (1), Pioglitazone (1)	Hypoglycaemia (2), Heart Failure (1), Urinary Tract infection (1)
Monoclonals	3	Afatanib (1), Penbrolizumab (1), Ruxolitib (1)	Liver toxicity (1), Pneomonitis (1), Sepsis (1)
Statins	2	Atorvastatin (1), Simvastatin (1)	Myopathy (2)
Levodopa	2	Co-beneldopa (1), Co-careldopa (1)	Postural Hypotension (2)
PTH[3] analogues	2	Alfacalcidol (1), Calcitriol (1)	Hypercalcaemia (2)
NSAIDs [4]	2	Naproxen (2)	ACS (1), GI Bleed (1)
Benzodiazepines	2	Lorazepam (1), Tempazepam (1)	Confusion (2)
Baclofen	1	Baclofen (1)	Consitpation (1)
Amitriptyline	1	Amitriptyline (1)	Confusion (1)
Leviteracitem	1	Leviterecitem (1)	Renal impairment (1)
Doxazocin	1	Doxazocin (1)	Postural hypotension (1)
Nefopam	1	Nefopam (1)	Delirium (1)
Quinnine	1	Quinnine (1)	Prolonged QTc (1)
Lithium	1	Lithium (1)	Lithium Toxicity (1)
Laxatives	1	Laxatives (1)	Diahrroea (1)
Bisphophanates	1	Alendronic Acid (1)	Erosive Gastritis (1)
Thyroxine	1	Levothyroxine (1)	Tachyarrythmia (1)
Zopiclone	1	Zopiclone (1)	Confusion (1)
Phosphodiesterase inhibitor	1	Uniphyllin (1)	Nausea (1)

(1) Angiotensin converting enzyme inhibitor (2) Angiotensin receptor blocker (3) Parathyroid hormone (4) Non steroidal anti inflammatory

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	4
		(*e*) Describe any sensitivity analyses	n/a

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	16
		(b) Indicate number of participants with missing data for each variable of interest	4
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*n/a*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*n/a*
		Cross-sectional study—Report numbers of outcome events or summary measures	*16*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16
		(*b*) Report category boundaries when continuous variables were categorized	16
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Additional

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Adverse drug reactions, multimorbidity and polypharmacy: A prospective analysis of one month of medical admissions

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Adverse drug reactions, multimorbidity and polypharmacy: A prospective analysis of one month of medical admissions

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ABSTRACT

Objective To ascertain the burden and associated cost of adverse drug reactions (ADRs), polypharmacy and multimorbidity through a prospective analysis of all medical admissions to a large University teaching hospital over a one-month period.

Design Prospective observational study.

Setting Liverpool University Hospital Foundation NHS Trust, England.

Participants All medical admissions with greater than 24-hour stay over a one-month period.

Main outcome measures Prevalence of admissions due to an ADR and associated mortality. Prevalence and association of multimorbidity and polypharmacy with ADRs. Estimated local financial cost of admissions where ADR was a contributing or main reason for admission with projected costs for NHS in England.

Results There were 218 identified patient admissions with an ADR giving a prevalence of 18.4%. The majority of these (90.4%) were ADRs that directly resulted in or contributed to admission. ADRs thus accounted for 16.5% of total admissions. Those with an ADR were on average taking more medicines (10.5 vs 7.8 $p<0.01$) and had more co-morbidities than those without an ADR (6.1 vs 5.2, $p<0.01$). Drugs most commonly implicated were diuretics, steroid inhalers, anticoagulants & antiplatelets, proton pump inhibitors, chemotherapeutic agents and antihypertensives. 40.4% of ADRs were classified avoidable or possibly avoidable. The mortality rate due to an ADR was 0.34%. The average length of stay for those with an ADR was 6 days. Direct one month cost to the Trust from ADR admissions was £490,716. Extrapolated nationally the projected annual cost to the NHS in England is 2.21 billion.

Conclusion The local prevalence of admission and mortality from ADRs are higher than previously reported. Important factors that could be contributing to this include polypharmacy and multimorbidity. ADRs place a significant burden on patients and healthcare services with associated financial implications. Reducing inappropriate polypharmacy should be a major aim for preventing ADRs.

Strengths and limitations of this study:

- Over 1000 medical admissions were individually reviewed by specialists in clinical pharmacology and general internal medicine in this prospective analysis of adverse drug reactions.
- Standardised criteria, as listed in methods, were used to identify and classify ADRs. This improves the objectivity and reproducibility of the analysis.
- Extrapolating the cost analysis nationally based on medical admissions locally may be unreliable due to differences including local population and services.
- This study does not take into account how commonly each medicine that caused an ADR is prescribed in the local community.

INTRODUCTION

Improved living conditions, and better access to and quality of medical care, has led to increased life expectancy and the associated accumulation of Long Term Conditions (LTC) [1]. According to a report by the Academy of Medical Sciences, multimorbidity is a growing issue globally, particularly in more economically developed countries where it is now considered the norm not the exception [2]. Age is the single biggest risk factor for LTCs such as cancer, cardiovascular disease and neurodegeneration in developed countries. An ageing population is therefore at increased risk of polypharmacy [3]. Care for people with multiple LTCs is often stretched across various single-organ specialists leading to siloed specialty prescribing and increasingly complex medication regimens.

Polypharmacy is the concurrent use of multiple medications by an individual. There is no consensus on the number of medications that defines polypharmacy because of the need to treat complex or multiple comorbidities with combinations of medicines. Thus, numerical definitions vary but perhaps the most common definition is taking 5 or more regular medications [4]. The Wessex Academic Health Science Network have developed a set of prescribing comparators to better understand both the numerical and risk-related factors involved in the variation of prescribing of multiple medicines [5]. In some individuals with complex or multiple conditions, polypharmacy may be appropriate, for example when medicines use has been individually optimised and prescribed according to best evidence. In contrast, potentially inappropriate polypharmacy, wherein the risk of harms from individual medicines may outweigh their benefit in the context of the prescription as a whole, is associated with poor adherence and an increased risk of adverse-drug reactions (ADRs) and interactions [6]. ADRs are an important cause of morbidity and mortality, with significant health implications and associated economic burden. Landmark studies in the USA in 1998 [7] and the UK in 2004 [8] found ADRs to be related to 6.7% and 6.5% of hospital admissions, respectively. More recent systematic reviews have reported figures ranging from 3.6% [9] to 15.6% [10]. Potential reasons for variation in findings include the heterogeneity of methodologies and populations studied.

Addressing avoidable ADRs due to inappropriate prescribing is important to reduce the burden on patients and healthcare systems. There are few adult observational studies of admission ADRs in the United Kingdom that are not focused on a specific populations or drug reactions. To our knowledge there are only 3 in the last 20 years [8,11,12]. In 2016, it was estimated that £1.3-3 billion could be saved in the NHS budget through reducing inappropriate and inefficient medicines usage[13].

The aim of this study was to determine the current impact of ADRs on medical admissions, their association with multimorbidity and polypharmacy, and quantify the economic impact on the

National Health Service (NHS). The population studied is broadly geographically comparable to that of Pirmohamed et al 2004 [8].

METHODS

Study data was collected for one month in the city centre site of the Liverpool University Hospital Foundation NHS Trust, a large teaching hospital in Merseyside, England. The research question was developed due to the impact ADRs have on patients by causing admissions to hospital. There were no patient contributors or co-authors in this study. Approval for this study was granted by Liverpool University Hospital Foundation NHS Trust clinical audit and service evaluation department (Project number 7580). All patients referred via the medical assessment unit that were admitted for >24 hours were included. These were mostly via the emergency department but also included primary care referrals and admissions from outpatient clinics. Patients admitted via medicine but transferred to other centres for emergency treatment (such as primary coronary intervention) within 24 hours were included, as their expected inpatient stay would be >24 hours. Information including e-notes, community drug prescriptions and investigations were reviewed to determine if an ADR occurred. An ADR was defined using the Edwards and Aronson criteria [14]. This does not include any type of drug overdose or relapse due to noncompliance. Cases were then defined as either the primary cause of admission, contributing factor or a co-incidental finding and assessed against the following criteria:

- Classification of the reaction as per Rawlins and Thompson [15] into Type A or Type B reactions.
- Causality as per the Liverpool causality assessment tool (LCAT) [16]. This is a validated method of assessing the causality of ADRs that can be used by groups or individuals.
- Severity as per the adapted Hartwig severity scale (AHSS) [17], a widely used tool that categorises ADRs from severity level 1 (requires no change in treatment) to level 6 (directly or indirectly resulted in patient death).
- Interactions as per the drug interaction probability scale (DIPS) [18]. DIPS assists practitioners in the assessment of drug interaction and evaluating causation in a specific patient.
- Avoidability as per the Liverpool ADR avoidability assessment tool (LAAT) [19]. This is a validated a tool to support the assessment of the avoidability of ADRs based on available patient information.

Factors that suggested an ADR include if it was consistent with the known adverse effect profile of the drug as per the British National Formulary [20], if there was a temporal relationship, and if alternate causes were excluded with history and investigation. Community drug prescription were verified and reviewed with patient electronic notes. This data was available for all admitted patients. If it was documented in the notes that a patient was not taking a medicine listed on their prescription this was not included in our analysis.

Identification of ADRs and subsequent assessment of the above criteria was completed by authors RO and LW. Where consensus was not reached it was assessed by third reviewer MP. Of the 258 patient episodes with possible identified ADRs, there was initial agreement on 236 (91%). For the remainder consensus was obtained following joint review with MP.

Patient Level Information and Costing System (PLICS) data reporting healthcare resource group and hospital costs were obtained from the Liverpool University Hospitals NHS Foundation Trust finance office. Total costs were summed for episodes of admitted care resulting from ADRs (a), and for all other admissions (where ADR was a contributory factor, coincidental, or unrelated; (b)). In order to extrapolate costs, totals for non-elective short and long stay, and regular day or night admissions, for NHS England (c), were obtained for 2018-19 [21]. Nationally projected costs were estimated as (a.c)/(a+b).

Patient and public involvement

The research question was developed due to the impact ADRs have on patients by causing admissions to hospital. There were no patient contributors or co-authors in this study.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SAS software (Version 9.4, SAS Institute, Cary, NC, USA). The results are presented either as means and standard deviations or frequencies and percentages. Associations between patient characteristics and admission type (ADR/Non-ADR) were investigated using univariable and multivariable logistic regression, with associations presented as odds ratios (OR) with 95% confidence intervals. The multivariable model used backwards selection with a probability of exclusion of 0.1. A P value < 0.05 was regarded as statistically significant.

RESULTS

There were 1,187 admissions with 218 patients with an ADR (18.4%). As some of those had multiple ADRs 235 were identified in total.

Characteristics of adverse drug reactions

145 (66.5%) of the ADRs were the primary cause of admission, with 51 (23.4%) contributing to admission, and 22 (10.1%) co-incidental findings that alone would not have required hospital stay. Thus, ADRs directly caused or contributed to 16.5% of all admissions. Using the Liverpool causality assessment tool [16] 45 (20.6%) were graded as definite, 79 (36.2%) as probable, and 94 (43.1%) as possible ADRs. 40 (18.4%) were graded as avoidable and 46 (21.1%) as possibly avoidable using LAAT criteria [19]. 64 (29.4%) of ADRs were possibly or probably cause by a drug-drug interaction as per DIPS[18]. 188 (86.2%) were Type A reactions as defined by Rawlins and Thompson[15] and 30 (13.8%) Type B. 164 (75.2%) of the ADRs were documented as recognised or acted on by the admitting medical team. The main drugs implicated in ADRs are listed in table 1. There were 4 ADRs (1.8%) that directly resulted in death and a further 5 that were implicated or a contributing factor to death (2.3%) (table 2). The mortality rate directly from ADRs, from all admissions, was therefore 0.42%. Median length of stay of patients with an ADR was 6 days.

Comparison of patients with and without adverse drug reactions

Table 3 shows descriptive statistics of patients with and without ADRs. In the patients with ADRs, as would be expected. liver and renal impairment were more prevalent compared to patients without ADRs (6.8% vs 2.8%, p 0.004),

Logistic regression results are presented in Table 4. Patients with ADRs were older than those without (mean age 73.2 (14.5) vs 66.7 (19.2), OR 1.02 (1.01, 1.03)) and were taking more medicines (mean 10.5 (4.6) vs 7.8 (5.1), OR 1.11 (1.07, 1.14)), with polypharmacy present in 91%, compared to 73% in the non-ADR group. They had more comorbidities (mean 6.1 (3.0) vs 5.2 (3.3), OR 1.08 (1.04, 1.13)), although this variable was not included in the multivariable model (due to its correlation with number of medicines). Those with ADRs were more likely to have liver impairment (6.9% vs 2.8%, OR 2.58 (1.35, 4.93)) and renal impairment (11.0% vs 6.8%, OR 1.69 (1.04, 2.78).

HRG costs were available for 214 (98.2%) patients in the ADR group, and 950 (98.0%) patients in the non-ADR group. Mean costs per episode of care were £2,293 (95% CI 1918, 2668) and £2,131 (95% CI 1899, 2364), respectively. The total costs of admissions resulting from ADR were £309,207, representing 12.3% of the costs of the whole cohort over the 1-month sampling frame. Admissions where ADR was a contributory factor cost £138,762 (5.5%); and where ADR was coincidental, the cost was £42,747 (1.7%). The total costs of non-elective short and long stays, and regular day or

night admissions across all NHS trusts and NHS foundation trusts in England was £17.98 bn in 2018-19, of which we estimate £2.21 bn were due to admissions resulting from ADRs.

DISCUSSION

This study found ADRs in 18.4% of hospital admissions. In 16.5% of admissions, it was the primary cause or a contributing cause suggesting ADRs have a significant burden on hospital admissions. This is over twice as high as the 6.5% found in Pirmohamed 2004 [8] which consisted of broadly the same geographical area. Most commonly implicated medicines included diuretics, steroid based inhalers, anticoagulants, proton pump inhibitors, antiplatelets, chemotherapy agents, anti-hypertensives, opiates and antidepressants/antipsychotics (Table 1). It is important to consider this study does not reflect how often each of these medicines are prescribed in the community. Some of the medicines implicated with the highest number of ADRs and deaths may be a reflection of how commonly they are prescribed. Furthermore, the use of these medicines also provides clinical benefits that reduce morbidity, mortality and need for hospital admissions, and this is not taken into account by our data. Direct mortality from ADRs was 0.42% which is also an increase from Pirmohamed 2004 (0.15%) [8] and twice as high as a recent meta-analysis [22].

Approximately, 40% of ADRs were classified as avoidable or possibly avoidable. This is consistent with previous studies which found significant proportions of ADRs that lead to hospital admissions are potentially avoidable [23]. Furthermore, as expected, the majority (86.2%) of ADRs were 'Type A' reactions meaning that they were the result of the expected pharmacological action of the medicine and therefore potentially more predictable and avoidable. Given this, future efforts should be targeted at reducing these preventable admissions. Key strategies that can mitigate for ADRs include stratifying patients by susceptibility prior to medication initiation using key information such as co-morbidities, concomitant medications and renal and hepatic function. This is particularly required in elderly patients who are at risk of accumulating multiple age-related health deficiencies that require drug therapy [24]. Where available and appropriate, pharmacogenomic testing can also be used to identify those at high risk of an ADR to guide medication choice, or optimal dose. Following initiation, management plans such as appropriate blood test monitoring and scheduled clinical review for ongoing indication can also reduce the risk of an ADR[25]. 29.4% of ADRs were possibly or probably caused by drug-drug interactions as per DIPS[18]. Deprescribing, defined as the process of dose-reduction or stopping of medicines by a healthcare professional, has been proposed as an important tool to reduce the burden of ADRs. The optimal use of medicines should include the

entire prescribing spectrum including starting, dose-adjustment and stopping at the point at which harm outweighs benefit.

Comparison with Pirmohamed 2004

Pirmohamed et al 2004 [8] was a large prospective study of admission ADRs in two Liverpool hospitals, the large university teaching hospital used in this study and a smaller district general hospital. This found an ADR prevalence in hospital admissions of 6.5%, suggesting there has been a significant increase since 2004. Numerous clinical reasons could have influenced this including changes in population demographics, increased morbidity and prescribing patterns. Some of the increase may be because pharmacovigilance has improved over the last 20 years, and the adverse reaction profile of drugs is more comprehensive. For example, following a large case control study by Ernst et al [26], an increased risk of pneumonia and dose dependant 30-day mortality from steroid based inhalers in COPD patients was added as a side effect to the British National Formulary. Over 10% of the ADRs in this study are attributable to this. Some ADRs were also secondary to newer therapies including chemotherapies and monoclonal antibodies that have been developed since 2004.

In 2004 two of the main causative medicines were NSAIDs (11.8%) and the antiplatelets (aspirin and clopidogrel) (23.8%). However, in this more recent study these medicines were implicated in only 0.85% and 7.4% of the ADRs respectively. Despite the increase in total ADRs from 2004 this would suggest a large proportional reduction. This could be due to greater awareness of these ADRs in older people leading to enhanced pharmacovigilance in prescribers along with changes in prescribing practice including co-administration of proton pump inhibitors (PPI). However, this change has promoted PPIs as a cause of ADRs from very few cases to being responsible for 12.1% of ADRs in this study. The majority of the reactions were only mild transient electrolyte disturbances, with only a single severe associated ADR of *Clostridium difficile*. In the case of anti-platelets, two factors are likely to have to contributed to this change: (a) there has been an active programme of reduction in their use for primary prevention of cardiovascular disease; and (b) changes in atrial fibrillation guidelines has led a greater use of anticoagulants rather than antiplatelets.

In recent years, concerns of an opiate crisis due to excessive community prescription has occurred in the USA [27]. In this study, opiate medications accounted for 5.1% of ADRs which is similar to the 6.0% found in 2004. This suggests that proportionally there has not been a significant increase in prescription opiate related admissions locally. Of the related 13 events, the majority were non-

lethal, with only 2 cases exhibiting respiratory depression but with no permanent harm following reversal.

Changes in prescribing patterns and subsequent ADRs may reflect increasing multimorbidity and polypharmacy. However, as such data was not previously collected this cannot be directly compared. Furthermore, methodological differences may have contributed as this study did not include any data from a district general hospital or surgical admissions. Additionally, screening and data collection was completed by medical doctors and clinical pharmacologists, whereas previously it was completed by a number of healthcare professionals. Thus, differences in clinical and diagnostic experience could also be responsible for some increased identification of ADRs. Finally, since 2004 Liverpool University Hospital Foundation NHS Trust has adopted electronic health records which may have assisted in the identification of ADRs in this study.

Multimorbidity and Polypharmacy

Multimorbidity and polypharmacy were both associated with admission ADR on univariate analysis. Those with an ADR were taking on average 35% more medicines than those without (10.5 v 7.8, p <0.001), which is an established risk factor for ADRs[28]. Despite this polypharmacy must not be conflated with inappropriate prescribing as some patients, particularly those that are multimorbid, require multiple medicines to optimise their LTCs with associated positive outcomes. This study did not assess the appropriateness of all community prescriptions, but only of those that directly caused an ADR via the avoidability assessment tool.

The mean number of comorbidities for the entire admitted population was 5.4. Although we do not have direct data from 2004 for comparison it is reported that the incidence of multimorbidity has been increasing [2]. The ADR group on average had 17% more co-morbidities than the non-ADR group (6.1 vs 5.2, p<0.001), which is a known risk factor [28]. However, the number of comorbidities was not part of the logistic regression because of the correlation between the number of medicines and number of co-morbidities. Although total number of co-morbidities is relevant, it does not to give insight into disease severity, for which the number of medications being taken may be a better proxy. For example, hypertension or type 2 diabetes managed with lifestyle factors would produce less medication burden than more advanced disease. Furthermore, some conditions and their management are known to predispose to prescribing cascades and therefore polypharmacy [28,29].

Cost analysis

ADRs are a significant cost burden on the NHS, and in this study accounted for £1 in every £8 spent on the care of non-elected hospital admissions. Put into perspective, the total cost of admissions

related to ADRs over the 1-month study period (£490,716) is comparable with the annual cost of chemotherapy procurement by the hospital in which the study was conducted. When extrapolated nationally, our estimate of £2.21 bn for admissions resulting from ADRs exceeds the costs of all outpatient procedures for NHS England. Previous cost analyses of medication-related harm in England provide annual estimates of £1.9 bn based on an extrapolation from Pirmohamed et al (2004)[30], £529m for potentially avoidable adverse drug reaction-related admissions [31], and £396m for discharged elderly people [32].

Strengths and weaknesses

Key strengths include that data was collected prospectively and notes were reviewed by specialists in clinical pharmacology and general internal medicine. This optimised the reliability of collected data and identification of ADRs. The availability of patient-level cost data, reflecting the actual spend on hospital care, represents another strength over many previous cost analyses.

Using standardised criteria to identify and classify ADRs improves objectivity and reproducibility as evidenced by levels of concordance >90% between reviewers. However, some elements of the criteria can be subjective and rely on reviewer clinical experience. Furthermore, many of the medical conditions and side effects attributed to an ADR may have occurred regardless of prescription, for example regarding steroid inhalers and the increased risk of pneumonia in COPD patients. A limitation of our study is that we have not concurrently assessed the benefits of taking medicines in individual patients.

It must be emphasised that causality assessment is a time-consuming process requiring clinical insight and therefore it is challenging to do this in time-limited real-world clinical practice. In the future, efforts to enhance the usability of electronic health care records, utilising time-saving approaches such as artificial intelligence and machine learning, could make medicines optimisation more efficient.

Liverpool is ranked as the most deprived major city in England, an established factor in predicting increased morbidity [32]. With the disparity between the most and least deprived areas in England having increased since the 1990's [33,34], changes in local population may have influenced differences found from 2004 as well as limit the utility of extrapolation of data nationally. In addition, generalisability of this data to more ethnically diverse populations is limited as Liverpool is 91% white.

CONCLUSION

This study found ADRs contributed or directly caused 16.5% of all admissions with an associated mortality rate of 0.34%. Factors associated with an ADR on logistic regression included age, number of medications and liver impairment. The data suggests ADRs place a significant and increasing burden on patients and healthcare services with associated financial implications. Using patient-level cost data the projected annual cost of ADR admissions to the NHS in England is £2.21 bn. With 39.4% of these ADRs identified as avoidable or potentially avoidable future efforts should be directed to reduce this burden. Reducing inappropriate polypharmacy should be a major aim for preventing ADRs.

DECLARATIONS

Competing interests

The authors have read the BMJ policy on declaration of interests and have nothing to declare.

Funding statement

MP receives research funding from various organisations including the MRC and NIHR. He has also received partnership funding for the following: MRC Clinical Pharmacology Training Scheme (co-funded by MRC and Roche, UCB, Eli Lilly and Novartis); a PhD studentship jointly funded by EPSRC and Astra Zeneca; and grant funding from Vistagen Therapeutics. He has also unrestricted educational grant support for the UK Pharmacogenetics and Stratified Medicine Network from Bristol-Myers Squibb and UCB. He has developed an HLA genotyping panel with MC Diagnostics, but does not benefit financially from this. He is part of the IMI Consortium ARDAT (www.ardat.org). None of these of funding sources have been used for the current paper.

There were no patient contributors or co-authors in this study.

Ethics approval

Approval was granted by Liverpool University Hospital Foundation NHS Trust clinical audit and service evaluation department (Project number 7580).

Data sharing

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis

Contributorship

Dr Rostam Osanlou undertook data collection, statistical analysis and wrote the initial draft of the paper. Dr Lauren Walker was involved in data collection, second reviewer and paper write up. Professor Dyfrig Hughes undertaking to the cost analysis in this study. Dr Girvan Burnside undertook statistical analysis of data and contributed to paper write up. Professor Sir Munir Pirmohamed came up with the idea, and was involved in assessing clinical cases and in reviewing the initial drafts and final draft of the paper.

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Tables

Table 1 – Drugs implicated in patient episodes with adverse drug reactions*

Drug class	No of ADRs (%)	Offending drug	ADR
Diuretics	31 (14.2%)	Furosemide (13), pironolactone (8), bumetanide (6), bendroflumethiazide (2), coamilofruse (1), indapamide (1)	Renal impairment (18), electrolyte derangement (12), postural hypotension (1)
Steroid inhaler	27 (12.4%)	Steroid inhaler (27)	Pneumonia (26), Oral Thrush (1)
Anticoagulants	21 (9.6%)	Warfarin (7), apixaban (5), edoxaban (4), rivaroxaban (4), enoxaparin (1)	Minor bleeding (10), anaemia (4), intracranial haemorrhage (4), Gastrointestinal bleed (3)
Proton pump inhibitor	18 (8.3%)	Lansoprazole (9), omeprazole (6), pantoprazole (3)	Hypomagnesaemia (11), hyponatraemia (6), C.Diff (1)
Antiplatelet	16 (7.4%)	Aspirin (13), clopidogrel (3)	Intracranial haemorrhage (5), Gastrointestinal bleed (4), minor bleeding (4), anaemia
Chemotherapy	16 (7.3%)	Chemotherapy (16)	Neutropenic Sepsis (8), Sepsis (4), Constipation (1), Deranged electrolytes (1), Rash (1), Thrombocytopenia (1)
ACE(1)-inhibitor / angiotensin receptor blocker	14 (6.4%)	Losartan (4), ramipril (4), irbesartan (3), candesartan (1), lisinopril (1), perindopril (1)	Renal impairment (9), postural hypotension (3), hyperkalaemia (1), renal failure (1)

Antidepressants & Antipsychotics	13 (6.0%)	Mirtazapine (2), sertraline (2), sulpride (2), carbemazapine (1), dosulepin (1), notriptyline (1), olanzapine (1), risperidone (1)	Confusion (3), hyponatraemia (3), parkinsonism (3), constipation (1), gastrointestinal bleed (1), prolonged QTc [2](1)
Opiates	13 (6.0%)	Codeine (5), morhpine sulphate (3), oxycodone (2), tramadol (2), buprenorphine (1)	Constipation (6), confusion (4), respiratory depression (2), hallucinations (1)
Other	49 (22.4%)	Other (49)	Other (49)
[1] Angiotensin converting enzyme [2] Corrected QT interval *In those with multiple ADRs only the most severe ADR was included in this table, as defined by the adapted Hartwig severity scale [16]. See supplementary material for full list.			

Table 2– Deaths directly related to the adverse reaction (Adapted Hartwig class 7b)

Medication	Number	Cause of death
Chemotherapy	2	Neutropenic sepsis (2)
Aspirin	1	Intracranial haemorrhage
Edoxaban	1	Gastrointestinal bleed

Table 3 – Characteristics of patients with and without adverse drug reactions

	ADR [(1)] group	Non ADR group	Total
Number of admissions	218	969	1187
Age Mean (s.d.)	73.2 (14.5)	66.7 (19.2)	67.9 (18.6)
Male (%)	106 (48.6%)	455 (47.0%)	561 (47.3%)
Number of medicines Mean (s.d.)	10.5 (4.6)	7.8 (5.1)	8.3 (5.1)
Polypharmacy (%)	199 (91.3%)	706 (72.9%)	905 (76.2%)
Number of co-morbidities Mean (s.d.)	6.1 (3.0)	5.2 (3.3)	5.4 (3.2)
Multimorbid (%)	99.1%	90.3%	91.9%
Liver impairment * (%)	6.9%	2.8%	3.5%
Renal impairment **(%)	11.0%	6.8%	7.6%

[(1)] Adverse drug reation
* Liver impairment defined as Chronic Liver Disease
** Renal impairment defined as Chronic Kidney Disease stage IV or V

Table 4: Logistic regression analysis of patients with and without adverse drug reactions

	Univariable odds ratio (95% CI)	p-value (Wald chi-square)	Multivariable odds ratio (95% CI)	p-value (Wald chi-square)
Age	1.02 (1.01, 1.03)	<0.001	1.02 (1.01, 1.03)	<0.001
Sex (Male)	1.07 (0.80, 1.44)	0.659		
Number of medicines	1.11 (1.07, 1.14)	<0.001	1.10 (1.07, 1.13)	<0.001
Number of comorbidities	1.08 (1.04, 1.13)	<0.001		
Liver impairment (CLD)	2.58 (1.35, 4.93)	0.004	3.23 (1.63, 6.40)	<0.001
Renal impairment (CKD stage 4 or 5)	1.69 (1.04, 2.78)	0.036		

Supplementary material - Full list of Adverse reactions by drug class

Drug Class	Number of associated ADRs	Medications implicated	Adverse reaction
Diuretics	31	Furosemide (13), Spironolactone (8), Bumetanide (6), Bendroflumethiazide (2), Coamilofruse (1), Indapamide (1)	Renal impairment (18), Electrolyte derrangement (12), Postural hypotension (1)
Steroid inhailer	27	Steroid inhailer (27)	CAP (26), Oral Thrush (1)
Anticoagulants	21	Warfarin (7), Apixaban (5), Edoxaban (4), Rivaroxaban (4), Enoxaparin (1)	Minor bleeding (10), Anaemia (4), Intracranial haemmhorage (4), GI bleed (3)
Proton Pump Inhibitor	18	Lansoprazole (9), Omeprazole (6), Pantoprazole (3)	Hypomagnasaemia (11), Hyponatraemia (6), C.Diff (1)
Antiplatlets	16	Aspirin (13), Clopidogrel (3)	Intracranial haemoorhage (5), GI bleed (4), Minor bleeding (4), Anaemia
Chemotherapy	16	Chemotherapy (16)	Neutropenic Sepsis (8), Sepsis (4), Constipation (1), Derranged electrolytes (1), Rash (1), Thromocytopenia (1)
ACE-I [(1)] /ARB [(2)]	14	Losartan (4), Ramipril (4), Irbesartan (3), Candesartan (1), Lisinopril (1), Perindopril (1)	Renal impairment (9), Postural hypotension (3), Hyperkalaemia (1), Renal failure (1)
Antidepressants & antipsychotics	13	Mirtazapine (2), Sertraline (2), Sulpride (2), Carbemazapine (1), Dosulepin (1), Notriptyline (1), Olanzapine (1), Risperidone (1)	Confusion (3), Hyponatraemia (3), Parkinsonism (3), Constipation (1), GI bleed (1), Prolonged QTc (1)
Opiates	13	Codeine (5), Morhpine Sulphate (3), Oxycodone (2), Tramadol (2), Buprenorphine (1)	Constipation (6), Confusion (4), Respiratory Depression (2), Hallucinations (1)
Beta adrenoceptor blockers	9	Bisoprolol (6), Atenolol (1), Nebivolol (1), Propanolol (1)	Bradycardia (5), Postural hypotension (4)
Insulin	7	Insulin (7)	Hypoglycaemia (4), Hypoglycaemic seizures (2)
Calcium Channel Blocker	6	Amlodipine (4), Ivabradine (1), Diltiazem (1)	Postural hypotension (5), Prolonged QTc (1)
Bladder anticholenergics	6	Solifenacin (4), Tolterodine (1), Tropsium (1)	Confusion (4), Constipation (2)
Immunosuprresants	5	MMF (3), Tacrolimus (2)	Sepsis (5)
Antimicrobials	4	Penicillin (2), Aciclovir (1), Azithromicin (1)	Angioedema (1), Rash (1), Renal impairment (1), Prolonged QTc (1)

Oral anti diabetics	4	Gliclazide (2), Empaglaflozin (1), Pioglitazone (1)	Hypoglycaemia (2), Heart Failure (1), Urinary Tract infection (1)
Monoclonals	3	Afatanib (1), Penbrolizumab (1), Ruxolitib (1)	Liver toxicity (1), Pneomonitis (1), Sepsis (1)
Statins	2	Atorvastatin (1), Simvastatin (1)	Myopathy (2)
Levodopa	2	Co-beneldopa (1), Co-careldopa (1)	Postural Hypotension (2)
PTH[3] analogues	2	Alfacalcidol (1), Calcitriol (1)	Hypercalcaemia (2)
NSAIDs [4]	2	Naproxen (2)	ACS (1), GI Bleed (1)
Benzodiazepines	2	Lorazepam (1), Tempazepam (1)	Confusion (2)
Baclofen	1	Baclofen (1)	Consitpation (1)
Amitriptyline	1	Amitriptyline (1)	Confusion (1)
Leviteracitem	1	Leviterecitem (1)	Renal impairment (1)
Doxazocin	1	Doxazocin (1)	Postural hypotension (1)
Nefopam	1	Nefopam (1)	Delirium (1)
Quinnine	1	Quinnine (1)	Prolonged QTc (1)
Lithium	1	Lithium (1)	Lithium Toxicity (1)
Laxatives	1	Laxatives (1)	Diahrroea (1)
Bisphophanates	1	Alendronic Acid (1)	Erosive Gastritis (1)
Thyroxine	1	Levothyroxine (1)	Tachyarrythmia (1)
Zopiclone	1	Zopiclone (1)	Confusion (1)
Phosphodiesterase inhibitor	1	Uniphyllin (1)	Nausea (1)

(1) Angiotensin converting enzyme inhibitor (2) Angiotensin receptor blocker (3) Parathyroid hormone (4) Non steroidal anti inflammatory

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	4
		(*e*) Describe any sensitivity analyses	n/a

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	16
		(b) Indicate number of participants with missing data for each variable of interest	4
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*n/a*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*n/a*
		Cross-sectional study—Report numbers of outcome events or summary measures	*16*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	16
		(*b*) Report category boundaries when continuous variables were categorized	16
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Additional

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.