Chronic condition comorbidity and multidrug therapy in general practice populations: a cross-sectional linkage study

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ABSTRACT

Objectives: The study investigated (1) the association between comorbidity and multidrug prescribing compared with the index condition, and (2) the association between vascular comorbidity and non-vascular condition key drug prescribing.

Design: Cross-sectional study linking anonymised computer consultations with prescription records for a 2-year time period.

Setting: 11 general practices in North Staffordshire, England.

Participants: Study groups aged 40 years and over (N=12 875). Within six conditions, comorbid group with the other five conditions was compared with an ‘alone’ group without them. Additionally, how the ‘vascular’ (one of diabetes, cardiovascular disease and cerebrovascular disease) comorbidity influenced chronic obstructive pulmonary disease (COPD), osteoarthritis (OA) or depression drug prescribing was investigated.

Outcome measures: Based on the British National Formulary, five main drug chapters constituted a measure of drug counts, with low count as 2 or less and high multidrug count as 3 or more. Key drugs prescribed for COPD, OA and depression were derived from guidelines.

Results: The adjusted associations between the comorbid groups and higher multidrug count compared with their respective ‘alone’ group were: odds ratio (OR) 7.1 (95% CI 5.6 to 9.0) for depression, OR 5.4 (95% CI 4.6 to 6.3) for cardiovascular disease, OR 3.7 (95% CI 2.8 to 5.0) for cerebrovascular disease, OR 3.6 (95% CI 3.1 to 4.3) for OA, OR 3.5 (95% CI 3.0 to 4.2) for diabetes and OR 3.2 (95% CI 2.6 to 4.0) for COPD. In COPD, vascular comorbidity was associated with a significant reduction in key COPD drug treatments (adjusted OR 0.6 (95% CI 0.4 to 0.7)). In depression, vascular comorbidity was associated with a reduction in key depression drug treatments (OR 0.6 (95% CI 0.4 to 0.7)).

Conclusions: Our findings show that multidrug prescribing for different body systems is higher with comorbidity and may be associated with lower likelihood of prescribing for specific conditions. Further research is required on whether multidrug prescribing influences the outcomes of care for chronic conditions.

Strengths and limitations of this study

The study was based on large-scale data linking common chronic conditions from general practice populations to prescription data over a 2-year time period.

The study highlights the innovative approach to multidrug measurement which accounts for vascular condition-specific drugs as well as summarising non-vascular codrug therapy.

The study provides the emergent approach to investigating the influence of multidrug therapy on potentially ‘optimal’ drug prescribing in populations.

The study uses a specific but limited number of common chronic conditions to illustrate the approach to linking comorbidity and multidrug data within a single large region of the UK.

The study used overall broad measures of drug prescribing and further research is required to understand the specific influence of multidrug dose and duration on longer term outcomes.

INTRODUCTION

Many older people experience two or more morbidities at the same time which is defined as multimorbidity, and within this comorbidity is defined as other co-occurring diseases in the same individual with an index condition.1–2 These are important concepts as the experience of multiple conditions at the same time may influence the progression and treatment of an index condition. Current evidence of the overall implications of chronic diseases has shown that this phenomenon is associated with adverse health, increased healthcare utilisation and increased mortality.3–5 Although the health impact of chronic disease comorbidity has been studied, there have been few studies on how chronic diseases comorbidity might influence drug use and related clinical decisions, especially in general practice. This is a significant evidence gap despite the fact that...
drug interventions feature routinely in many disease guidelines. Currently, the model for managing chronic diseases focuses on treating individual conditions, and patients may on the one hand benefit from the drug treatment of each of their chronic conditions; however, there is a risk of multiple drug therapy, side effects and drug interactions which could in combination be detrimental. 

Many national healthcare policies have developed frameworks for chronic disease models of care and specific guidelines for the optimal management of chronic diseases. Examples include policy and guidelines for the common conditions in the general population with diabetes, ischaemic heart disease, stroke, chronic obstructive airways disease and depression. In addition, these guidelines are beginning to be adapted for the common experience of comorbid conditions, particularly by older people, for each of these individual conditions. Since people with one or more chronic conditions are increasing in number, this has increasingly brought in focus the scale and quantity of multiple drug prescribing in general populations. The key questions then become (1) how does multiple drug prescribing for different systems relate to the primary index condition and (2) how does multiple drug prescribing escalate when populations experience multiple conditions which might be directly linked or occur by chance together. The cardiometabolic diseases, such as hypertension, diabetes, heart disease and cerebrovascular disease, share aetiology and common drug treatment pathways, but it is still important to understand the scale of multiple drug therapy that might be associated when these conditions co-occur together in the same individual. Many chronic diseases also have conditions which are related to mechanisms other than pathophysiology. For example, other common chronic conditions include chronic obstructive airways disease and depression, and this epidemiology provides the scale of multiple drug therapies when co-occurring conditions might be unrelated.

In terms of the current evidence in this field, much of it has focused around ‘polypharmacy’ studies. However, while this might seem an appropriate broad umbrella term, in research and clinical approaches, it has often focused on arbitrarily chosen number of drugs, and linked the term to either inappropriate prescribing or associated adverse events in older populations. This lack of consensus defined approach to this problem has led to an argument for less ambiguous terminology, and we propose that ‘multidrug’ therapy is used to link in with the standard approach to two or more conditions, which is ‘multimorbidity’. Within this evidence, there is still a clear gap in how morbidity link to drug prescribing, and whether comorbidity influences the drug prescribing for an index disease.

In this study, the focus was on six common chronic conditions in the general population, which included diabetes mellitus, cardiovascular diseases, cerebrovascular diseases, chronic obstructive pulmonary diseases (COPD), osteoarthritis (OA) and depression. The choice of these chronic conditions for the purpose of the study was based on a number of factors including the epidemiology, especially prevalence of the diseases, as well as aetiopathogenesis and impacts on quality of life and psychological well-being. For example, while diabetes mellitus, coronary heart disease and cerebrovascular diseases have a common pathological basis of causation (the ‘vascular group’), and often coexist in one patient, they are also known to have high mortality rates—hence the drive towards measures aimed at optimising the management of these diseases. The other three non-vascular chronic conditions—COPD, OA and depression—are leading causes of morbidity, high cost of care and psychological distress, respectively. The rationale for our focus on few selected common conditions was also to provide common comorbidity combinations which are potentially treated with drugs as a key intervention.

We investigated two separate issues using the selected group of vascular and non-vascular conditions. First, we wanted to investigate the relative multidrug prescribing for each of six chosen index examples, comparing comorbid groups with prescribing levels in the respective index groups. Second, we wanted to test whether vascular comorbidity influenced key drug prescribing for chosen conditions. The vascular group was likely to be on similar multiple drugs, so the distinct hypothesis was tested, that was drug prescribing in vascular conditions overall may influence key drug prescribing in the individual non-vascular conditions of COPD, OA or depression.

METHODS
Design and study population
The cross-sectional study was conducted using two linked databases on patients aged 40 years and over presenting to general practice over a 2-year time period (from 1 January 2002 to 31 December 2003). We wanted to investigate what multidrug prescribing levels were before a national UK performance-based incentive (Quality outcomes framework) was implemented to test the associations between comorbidity and routine multidrug prescribing.

Settings
The clinical and prescription databases analysed were derived from an anonymised computer-recorded consultations from 11 general practices from the North Staffordshire Keele GP research partnership. The partnership covers a range of practices covering varying socio-economic groups within rural and urban areas and has been involved in data collection over time for the purpose of epidemiological studies. There is an ongoing process of data validation to improve data quality, and there is evidence that this measure improves data recording by general practitioners (GPs) and their teams.
Chronic disease data
The Consultation in Primary Care Archive (CiPCA) database focuses on the routinely collected morbidity encounters in actual consultations and coded using a standard clinical classification (READ codes). Patients who had a record of a disease-specific READ coded morbidity of interest were included in the study and the main codes were used with all associated ‘daughter codes’. The main READ codes that were used to define the chronic disease groups were: diabetes mellitus (READ codes C10), cardiovascular diseases (ischaemic heart disease (G3); heart failure (G58), excluding hypertension), cerebrovascular diseases (G6), COPD (H30, excluding asthma), OA (N05, excluding arthralgia) and depression (E11, E20, Eu and excluding psychosis).

Comorbidity: definitions
There were two approaches to defining comorbidity. First, comorbidity was defined as the presence of one of the other five selected conditions. So using the diabetes population as an example, the diabetes ‘index’ group was defined as diabetes ‘alone’ and without anyone of the other five conditions, whereas diabetes ‘comorbid’ group was defined as at least one of the other five conditions. The index ‘alone’ group would also enable the capture of the other morbidity that was outside of the ones within the study. This definition was applied to each of the six chronic conditions individually. Second, in the vascular group, comorbidity was defined separately as the individual and specific addition of COPD, OA or depression, and irrespective of whether the latter three occurred together.

Prescribed drug measure: overall multidrug count definitions
The Prescriptions in Primary Care Archive (PiPACA) database focuses on the routinely collected prescribed medications and which were coded using the British National Formulary (BNF) classification. The BNF consists of 15 main chapters based on the systems of the body, and within which there are further subsections for specific clinical indications. Only patients on repeat drug prescriptions were selected for defining measures because this gives a better representation of multiple drugs used on a long-term basis for the majority of patients with chronic conditions.

Specific drug treatment chapters for the six chronic diseases of interest in the study were identified and used as a summary of multidrug counts. The BNF chapter for cardiovascular and cerebrovascular drugs was under BNF chapter 2, for COPD drugs under chapter 3, for depression under chapter 4, for diabetes mellitus under chapter 6 and for OA under chapters 4 and 10. This means that overall, there were five main BNF chapters, which could constitute a measure of drug counts of up to a total of 5. The multidrug count definition in this approach would then specifically relate to people prescribed drugs from at least two or more of the five chapters indicated.

Vascular comorbidity and drug prescribing for non-vascular conditions
The key likelihood of receiving drug treatments for the specific conditions of COPD, OA and depression in the study population with vascular comorbidity was also investigated. In this approach, the ‘vascular’ comorbidity was defined as the group any one of diabetes, cardiovascular disease and cerebrovascular disease. The non-vascular groups were then individually compared with and without vascular comorbidity. For example, the COPD group was compared with vascular comorbidity to the COPD without vascular comorbidity, in relation to the likelihood of receiving COPD-specific drug treatment.

While the key drug treatments for COPD, OA and depression can be examined in different ways such as the use of specific drugs, or drug doses and duration of drug therapy, we wanted to first establish the simplest likelihood of a patient given one of the key group of drugs for COPD, OA or depression. The group of drugs derived from guidelines for COPD included bronchodilators, corticosteroids, inhaled steroids and oxygen (BNF sections 3.1, 3.2, 3.5 and 3.6). The group of drugs for OA included non-opioid analgesics, opioid analgesics, non-steroidal anti-inflammatories and Cox 2 inhibitors (BNF sections 4.7.1, 4.7.2, 10.1.1 and 10.1.2.2). The group of drugs for depression included hypnotics, anxiolytics and antidepressants (BNF sections 4.1 and 4.3).

Analysis
The first analysis was to describe the 2-year period prevalence of the five main BNF chapters in the specified chronic disease population, with a focus on some of the common drugs that were prescribed within each chapter expressed as drug prevalence/10 000 population aged 40 years and over, and differences were assessed using χ² tests. The five main chapter drug categories prevalence is described by age, gender and deprivation status. Deprivation was measured by the Index of Multiple Deprivation (IMD) which is a composite score that is linked to postal address codes. The IMD score was categorised into the bottom 20% (most deprived), middle 60% and the top 20% score (most affluent).

For each of the six chronic conditions, associations between the comorbid groups and higher multidrug counts were compared with the respective reference ‘alone’ group. The ‘outcome’ of higher multidrug therapy was defined as 3 or more of the chapter counts and compared with 2 counts or less. Associations using logistic regression were expressed as ORs with 95% CIs, and also included the ratios comparing prevalence of each drug count category in the comorbid group compared with the ‘alone’ group. Then for the vascular group, associations between each of the comorbid group

Roberts ER, et al. BMJ Open 2014;4:e005429. doi:10.1136/bmjopen-2014-005429

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with COPD, OA or depression were compared with the vascular ‘alone’ alone, and higher multidrug counts were then estimated.

Finally, the data were analysed for the study defined optimal drug treatments for COPD, OA or depression. Three study groups constructed were: COPD with at least one of the vascular conditions; OA with at least one of the vascular conditions and depression with at least one of the vascular conditions. Each group was then compared to their respective vascular group, for example, COPD and vascular group compared with COPD without a vascular condition, by the specific optimal drug treatment. Association estimates using logistic regression are presented as unadjusted and adjusted figures with 95% CIs. Analyses were carried out using SPSS V.17.0 statistical software.

RESULTS

Study population
In the study population of 12 875 aged 40 years and over, the numbers of patients prescribed with cardiovascular system drugs were 9384 (2-year time period prevalence 73%), respiratory system drugs were 2861 (22%), non-opioid analgesia were 5395 (42%), antidepressants were 3241 (25%), antidiabetic drugs were 2916 (23%) and musculoskeletal system anti-inflammatory drugs were 2143 (17%; table 1).

In terms of the sociodemographic distribution, older patients aged 70 years and over and populations in the top 20% most deprived status were significantly more likely to be prescribed all main drug categories, except for the cardiovascular system ($\chi^2$ test for trend p<0.001). For women compared with men, there was variation by type of main drug category; the comparative 2-year prevalence figures by gender were significantly higher for men compared with women for the cardiovascular system drugs (76% vs 70%) and diabetes (26% vs 20%), but similar for COPD (p=0.462). Prevalence figures were lower for men compared with women for anxiolytics and antidepressants (49% vs 66%) and anti-inflammatoryatories (15% vs 18%; $\chi^2$ test p<0.001; table 2).

Individual chronic condition comorbidity and higher multidrug counts
For all six specified chronic conditions, at lower drugs counts of up to 2, the prevalence numbers were greater for the individual groups without the other five comorbid conditions compared with the numbers for the individual conditions with comorbidity of other five conditions (table 3). For the drug count of 2 different chapters, the comorbid to ‘alone’ ratios ranged from 1.15 for the depression group to 0.5 for the diabetes group. The prevalence ratios were highest for the multidrug count of 4, and these ranged from 13.7 for the depression comorbid group to 2.3 for the diabetes comorbid group.

Adjusting for age, gender and deprivation, the associations between the comorbid groups and higher multidrug count compared with their respective ‘alone’ group ordered by strength of association were: OR 7.1 (95% CI 5.6 to 9.0) for depression, OR 5.4 (95% CI 4.6 to 6.3) for cardiovascular disease, OR 3.7 (95% CI 2.8 to 5.0) for cerebrovascular disease, OR 3.6 (95% CI 3.1 to 4.3) for OA, OR 3.5 (95% CI 3.0 to 4.2) for diabetes and OR 3.2 (95% CI 2.6 to 4.0) for COPD.

Vascular condition comorbidity and higher multidrug counts
The prevalence ratios for the multidrug count of 5 ranged from 3.9 for vascular group comorbid with OA to 1.9 for vascular group comorbid with COPD and 1.0 for the vascular group comorbid with depression (table 4). Adjusting for age, gender and deprivation, the associations between the comorbid groups and higher multigroup count compared with their respective ‘alone’ group ordered by strength of association were: OR 4.6 (95% CI 3.8 to 5.7) for vascular group comorbid with COPD, OR 3.2 (95% CI 2.6 to 3.9) for vascular group comorbid with depression and OR 3.0 (95% CI 2.6 to 3.5) for vascular group comorbid with OA.

Comorbid vascular conditions and optimal non-vascular condition prescribing
The three specific non-vascular groups of COPD, OA and depression were compared with comorbid vascular conditions to without such vascular comorbidity in terms of their respective optimal drug treatment (table 5). Adjusting for age, gender and deprivation, the association between the COPD and vascular comorbid groups compared with their respective group without vascular conditions showed a significant reduction in optimal COPD drug treatment with an OR of 0.6 (95% CI 0.4 to 0.8). Adjusting for age, gender and deprivation, the association between the depression and vascular comorbid groups compared with their respective group without vascular conditions showed a significant reduction in optimal depression drug treatment with an OR of 0.6 (95% CI 0.4 to 0.7). Adjusting for age, gender and deprivation, the association between the OA and vascular comorbid groups compared with their respective group without vascular conditions did not show a statistically significant reduction in optimal OA drug treatment with an OR of 0.8 (95% CI 0.6 to 1.1).

DISCUSSION
Our findings from a large cross-sectional study of nearly 13 000 patients aged 40 years and over with one of six specified and common chronic conditions showed the scale of multidrug prescribing, which was higher in the presence of comorbidity compared with the respective index groups. While previous evidence has shown the high levels of multiple drug prescribing, our study

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findings link the disease and comorbidity status to the measure of multidrug prescribing for different systems. Depending on whether the chronic conditions were vascular (diabetes, cardiovascular or cerebrovascular) or non-vascular (COPD, OA or depression), the higher levels of multidrug prescribing varied. All six conditions with comorbidity compared with their index condition had much higher multidrug count, even adjusting for age, gender and deprivation. The measure of multidrug count was notably distinct by the use of five different main drug chapter categories which were for different body systems, which means that this ‘outcome’ was not about multiple drug use for the same condition. For example, a diabetic with a higher multidrug count of 4 or 5 in this study relates to different and distinct body systems, and not to the different drugs under the same chapter. The chronic condition of depression comorbidity had the strongest strength of association with higher multidrug counts, followed by cardiovascular disease comorbidity, and the estimates of association for cerebrovascular disease, OA and diabetes were similar. These findings suggest that the index condition and associated comorbidity may influence the range of multidrug prescribing, and generates the interesting hypothesis that potential variation in clinical outcomes of the index conditions is as a result of underlying comorbid drug prescribing.

The study also grouped the vascular-related conditions to investigate the influence of non-vascular drug prescribing compared with vascular conditions ‘alone’ (ie, without any one of COPD, OA or depression). Again, the adjusted associations were significant, with vascular comorbidity being associated with higher multi drug counts compared with the respective ‘vascular index’ group. Here the clinical implication is that vascular comorbidity in populations aged 40 years and over might not only be associated with multiple vascular drugs as routinely suggested by clinical guidelines, but

| BNF chapter | BNF subsections | BNF classification | Drug examples | Number | Drug prevalence/10 000† |
|-------------|-----------------|--------------------|---------------|--------|------------------------|
| 2 Cardiovascular system | 2.9 | Antiplatelet drugs | Aspirin, clopidogrel, dipyridamole | 9384 | 7289 |
| | 2.8 | Anticoagulants | Warfarin | 5044 | 3918 |
| | 2.2 | Diuretics | Thiazide diuretics | 669 | 520 |
| | 2.4 | β-blockers | Bisoprolol | 4912 | 3815 |
| | 2.5 | ACE inhibitors or ARB | Ramipril, candesartan | 4034 | 3133 |
| | 2.6 | nitrates, calcium antagonists | GTN, amloidipine | 4250 | 3301 |
| | 2.12 | Lipid regulating drugs | Simvastatin | 4984 | 3817 |
| 3 Respiratory system | 3.1 | Bronchodilators | Salbutamol | 2861 | 2222 |
| | 3.2 | Corticosteroids | Beclomethasone | 2775 | 2155 |
| | 3.6 | Oxygen | NA | 2140 | 1662 |
| 4 Central nervous system drugs | 4.7.1 | Non-opioid analgesics | Paracetamol | 3241 | 2517 |
| | 4.7.2 | Opioid analgesics | Codeine, tramadol | 3241 | 2517 |
| | 4.1 | Hypnotics and anxiolytics | Diazepam | 2916 | 2265 |
| | 4.3 | Selective serotonin reuptake inhibitors | Fluoxetine, citalopram, amitriptyline | 632 | 491 |
| 6 Endocrine system | 6.1.1 | Insulin | Insulin, humalog | 2334 | 1805 |
| | 6.1.2 | Oral antidiabetic drugs | Metformin, gliclazide | 2143 | 1664 |
| 10 Musculoskeletal and joint disease | 10.1.1 | Non-steroidal anti-inflammatory drugs | Ibuprofen, cyclooxygenase inhibitors | 2143 | 1664 |

†Population refers to those with one of six chronic conditions (n = 12 875), which included hypertension, diabetes, coronary heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, osteoarthritis and depression; drug categories are based on the BNF classification.
ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blockers; BNF, British National Formulary; GTN, glyceryl trinitrate; NA, not applicable.
by a range of conditions such as comorbidity of COPD, OA or depression. It is possible that these conditions and the drug treatments for them may also in the end influence the health and healthcare outcomes of the index vascular conditions.29

In terms of the influence of comorbidity on key drug prescribing, our study findings show that vascular comorbidity in COPD and depression is associated with lower likelihood of drug prescribing for the respective conditions of COPD and depression. Similar findings, particularly for suboptimal depression drug treatment, when depression is comorbid with chronic disease have been shown previously.30 31 However, such findings for OA were not found, and here it is possible that the study definition of analgesia was too broad, as analgesia use covers a range of other painful conditions, in addition to OA. Although the key drug definition was simple and broad, our study findings seem to suggest that comorbidity does influence drug prescribing for specific conditions. Whether this is due to some kind of therapeutic inertia or is due to GPs’ reasoned consideration of drug–drug and drug–disease interactions and the overall

| Table 2 | Sociodemographic characteristics of the main drug categories |
| --- | --- |
| Factor | Total numbers | Cardiovascular system | Respiratory system | Central nervous system | Endocrine system | Musculoskeletal system |
| Age (years) | | | | | | |
| 40–54 | 2738 | 1257 (46) | 441 (16) | 1447 (53) | 555 (20) | 378 (14) |
| 55–69 | 4963 | 3712 (75) | 1131 (23) | 2694 (54) | 1250 (25) | 1003 (20) |
| 70–84 | 4459 | 3807 (85) | 1154 (26) | 2824 (63) | 1010 (23) | 703 (16) |
| 85 and over | 715 | 608 (85) | 135 (19) | 513 (72) | 101 (14) | 59 (8) |
| Gender | | | | | | |
| Women | 6896 | 4813 (70) | 1510 (22) | 4528 (66) | 1351 (20) | 1260 (18) |
| Men | 5979 | 4571 (76) | 1351 (23) | 2950 (49) | 1250 (25) | 883 (15) |
| Deprivation* | | | | | | |
| Deprived status | 2609 | 1952 (75) | 780 (30) | 1705 (65) | 695 (27) | 474 (18) |
| Middle status | 7228 | 5308 (73) | 1538 (21) | 4184 (58) | 1616 (22) | 1223 (17) |
| Affluent status | 2203 | 1584 (72) | 354 (16) | 1185 (54) | 419 (19) | 377 (17) |

*Deprivation measured by Index of Multiple Deprivation, figures in brackets refer to the percentage of each study factor subgroup.

| Table 3 | Associations between individual study groups and higher multidrug counts |
| --- | --- |
| Conditions | Multidrug number/10 000 population |
| | 0 | 1 | 2 | 3 | 4 | 5 | Adjusted OR (95% CI) |
| Diabetes 'alone'* | 239 | 1178 | 4332 | 3120 | 1021 | 110 | 1.0 |
| Diabetes comorbidity | 58 | 492 | 2208 | 4523 | 2353 | 366 | 3.50 (3.0 to 4.2) |
| Prevalence ratio† | 0.2 | 0.4 | 0.5 | 1.5 | 2.3 | 3.3 |
| CHD 'alone'* | 148 | 4057 | 4248 | 1372 | 160 | 16 | 1.0 |
| CHD comorbidity | 36 | 1027 | 3973 | 3516 | 1327 | 121 | 5.35 (4.6 to 6.3) |
| Prevalence ratio† | 0.2 | 0.3 | 0.9 | 2.6 | 8.3 | 7.6 |
| CVD 'alone'* | 688 | 4087 | 3848 | 1306 | 70 | 1.0 |
| CVD comorbidity | 41 | 1745 | 4251 | 3224 | 678 | 62 | 3.70 (2.8 to 5.0) |
| Prevalence ratio† | 0.1 | 0.4 | 1.1 | 2.5 | 9.7 | NA |
| COPD 'alone'* | 940 | 2487 | 3496 | 2726 | 350 | 0 | 1.0 |
| COPD comorbidity | 189 | 946 | 2855 | 4117 | 1751 | 142 | 3.22 (2.6 to 4.0) |
| Prevalence ratio† | 0.20 | 0.4 | 0.8 | 1.5 | 5.00 | NA |
| OA 'alone'* | 1378 | 2786 | 3722 | 1854 | 256 | 5 | 1.0 |
| OA comorbidity | 174 | 1260 | 3550 | 3420 | 1325 | 271 | 3.64 (3.1 to 4.3) |
| Prevalence ratio† | 0.1 | 0.5 | 1.0 | 1.8 | 5.2 | 54 |
| Depression 'alone'* | 1912 | 4140 | 3093 | 776 | 79 | 0 | 1.0 |
| Depression comorbidity | 325 | 1422 | 3555 | 3555 | 1082 | 62 | 7.11 (5.6 to 9.0) |
| Prevalence ratio† | 0.17 | 0.34 | 1.15 | 4.58 | 13.7 | NA |

*Alone—people with disease alone and none of the other five morbidities, comorbidity is 1 or more of other five study morbidities.
†Prevalence ratio=2-year drug count prevalence in the comorbid group/2-year drug count prevalence in the disease alone group; adjusted for age, gender and deprivation and estimates are with the ‘outcome’ of higher drug count (3–4 combined) compared to lower drug counts (2 or less)
CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; NA, not applicable; OA, osteoarthritis.
well-being of the patient is the important question raised by the findings.

The approach taken to look at specific groups and six common conditions was based on a combination of clinical rationale and feasibility. While, one could have investigated any number of combinations of the six conditions, the better and preferred approach taken was to group conditions first at the ‘vascular’ level. As highlighted earlier, diabetes, ischaemic heart disease and cerebrovascular disease have shared pathogenesis and there may be overlapping of drug treatments. However, the ‘non-vascular’ group constitutes individual chronic conditions with distinct and unrelated drug treatments. This approach enabled comorbidity definitions based on (1) group-level, that is, vascular comorbidity with one of the non-vascular conditions and (2) counts, that is, number of other conditions for each of the six index groups. The study focus was also on comorbidity and further research is also required on how multimorbidity, defined as two or more conditions, influences and multistable prescribing do offer clinical implications as outlined earlier. However, the implications of the associations between comorbidity and the key drug definitions may be limited in this cross-sectional design and these may be treated cautiously as emergent findings. The chronic disease definitions were also based on routinely collected registers from general practices, which were and are part of a research network dedicated to the collection of clinical data in actual consultation. While these chronic disease registers may be subject to variations in recording, the study analyses provide the estimates of association in actual clinical practice across 11 different sites.

The drug definitions were based on routinely coded repeat prescriptions and over a 2-year time period represent an appropriate measure at the simpler but distinct broad system category. Patients however will also have been prescribed other drug categories outside of the five main categories that we had selected and for other less common conditions from the ones selected in the study, which means these drug levels are a specific estimate. The construction of our study defined index or ‘alone’ groups (without the other five conditions) provided the relative multidrug level estimates to when the index condition was comorbid with one of the other five conditions. So the multidrug levels in the ‘alone’ group provide an estimate of main drug system prescribing without the associated condition (ie, for other indications) compared to levels when there is a clear

| Conditions | Multidrug number/10 000 population | Adjusted OR (95% CI) |
|------------|-----------------------------------|---------------------|
| Vascular group only* | 199 2373 4018 2547 773 89 | 1.0 |
| Vascular group and COPD | 85 677 2854 4207 2008 169 | 4.63 (3.8 to 5.7) |
| Prevalence ratio | 0.43 0.29 0.71 1.65 2.60 1.90 | |
| Vascular group and OA | 29 873 3493 3697 1557 349 | 3.01 (2.6 to 3.5) |
| Prevalence ratio | 0.15 0.37 0.87 1.45 2.01 3.92 | |
| Vascular group and Depression | 69 829 3733 3917 1359 92 | 3.22 (2.6 to 3.9) |
| Prevalence ratio | 0.35 0.35 0.93 1.54 1.76 1.03 | |

*Vascular group only is the reference group without COPD, OA or depression; prevalence ratio is comparing vascular comorbid group with vascular group alone for each drug count category, adjusted for age, gender and deprivation and estimates are with the ‘outcome’ of higher drug count (3–4 combined) compared with lower drug counts (2 or less).

COPD, chronic obstructive pulmonary disease; OA, osteoarthritis.

| Conditions | Key drug treatments* | No | Yes | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|------------|---------------------|----|-----|------------------------|---------------------|
| COPD without vascular comorbidity | 123 (22) | 937 (88) | 1.0 | 1.0 |
| COPD and vascular comorbidity | 87 (19) | 382 (81) | 0.58 (0.43 to 0.78) | 0.55 (0.40 to 0.75) |
| OA without vascular comorbidity | 281 (16) | 1440 (84) | 1.0 | 1.0 |
| OA and vascular comorbidity | 117 (17) | 568 (83) | 0.95 (0.75 to 1.20) | 0.82 (0.64 to 1.06) |
| Depression without vascular comorbidity | 259 (16) | 1378 (84) | 1.0 | 1.0 |
| Depression and vascular group | 120 (28) | 311 (72) | 0.49 (0.38 to 0.62) | 0.55 (0.42 to 0.73) |

*Drug treatment for COPD, OA or depression, respectively, adjusted for age, gender and deprivation as measured by Index of Multiple Deprivation.

COPD, chronic obstructive pulmonary disease; OA, osteoarthritis.

Table 4  Associations between vascular comorbidity groups and higher multidrug counts

Table 5  Key drug treatments of non-vascular conditions in vascular comorbidity
comorbidity record. However, this is time defined by a
2-year time window, so some misclassification may be
possible and further research could explore how broad
system drug definitions capture the underlying and spe-
cific common diagnostic categories. Further research is
also required for the arguably more complex assimilation
of the range of defined drug categories, other multimor-
bdity and to investigate specific effect of individual drug
categories. Most of these drugs, other than analgesics such
as anti-inflammatories, are not available over-the-counter
and are usually clinician prescribed. So it is possible that
common over-the-counter drugs, particularly in relation
to OA, may be an underestimate; however, the selection
of repeated prescribing would mitigate against such
underestimation. Finally, although a large scale study,
these general practices are drawn from one region of
England, and while this might limit generalisability, the
internal validity of the findings still remains.

In conclusion, our study shows the links
between common chronic conditions, comorbidity and
associated multidrug prescribing. The key and distinct
finding is that the study shows that multidrug prescrib-
ing defined by a range of selected but different systems
is high in chronic conditions and higher in comorbidity.
The common groups of vascular conditions are not the
only ones associated with their ‘own’ guideline driven
multidrug therapy, but the addition of non-vascular con-
ditions such as COPD, OA and depression adds to the
multidrugs burden in patients. The importance of these
findings, in addition to quantifying the scale, is whether
such multidrug therapy influences the quality of care for
each of the individual conditions. Our findings suggest
that the potential for suboptimal drug treatment as a
consequence is in line with other evidence and further
research is required to investigate the impact of disease
status, comorbidity, multidrug therapy on prospective
and long-term outcomes of clinical care.

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**Contributors** ERR and DG coordinated the study data collection
and contributed to the writing of the manuscript. ER, DS and UTK were involved
in study design and developed the statistical approaches. UTK conceived and
designed the study, was involved with analysis, interpretation and contributed
to the writing of this manuscript. All authors have contributed and approved
the final version of this manuscript.

**Funding** This work was funded by a National Institute for Health Research
(NIHR) In-Practice Fellowship for ERR and a NIHR School for Primary Care
Research Doctoral Training Studentship for D.J.G. Cipca and Pipca databases
were funded by the North Staffordshire Primary Care Research Consortium
and Keele University Institute for Primary Care and Health Sciences. This
report presents independent research commissioned by the NIHR. The views
expressed are those of the authors and not necessarily those of the NHS, the
NIHR or the Department of Health.

**Competing interests** None.

**Ethics approval** North Staffordshire Ethics Committee.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

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**REFERENCES**

1. Feinstein AR. The pre-therapeutic classification of co-morbidity in
chronic disease. J Chronic Dis 1970;23:455–88.
2. van den Akker M, Buntinx F, et al. Comorbidity or multimorbidity
what’s in a name? A review of literature. Eur J Gen Pract
1996;2:65–70.
3. Prior JA, Jordan KP, Kadum AT. Influence of chronic diseases on
long-term change in physical health: a consultation-survey linkage
cohort study in general practice. Qual Life Res 2012;21:881–91.
4. Kadum UT, Uttlley J, Jones PW, et al. Chronic disease multimorbidity
transitions across healthcare interfaces and associated costs: a
clinical-linkage database study. BMJ Open 2013;3 pii: e003109.
5. Fillenbaum GG, Pieper CF, Cohen HJ, et al. Comorbidity of five
chronic health conditions in elderly community residents:
determinants and impact on mortality. J Gerontol A Biol Sci Med Sci
2000;55:M84–9.
6. Haiden SJ, Johnell K, Thorslund M, et al. Trends in polypharmacy
and potential drug-durg interactions across educational groups in
elderly patients in Sweden for the period 1992–2002. Int J Clin
Pharmacol Ther 2007;45:643–53.
7. Kadum UT. Potential health impacts of multiple drug prescribing for
older people: a case-control study. Br J Gen Pract 2011;61:128–30.
8. Urso SC. Using clinical guidelines designed for older adults with
diabetes mellitus and complex health status. JAMA 2006;295:
1935–40.
9. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for
secondary prevention for patients with coronary and other
atherosclerotic vascular disease: 2006 update endorsed by the
National Heart, Lung, and Blood Institute. Circulation
2006;113:2363–72.
10. National Collaborating Centre for Chronic Conditions. Stroke:
national clinical guideline for diagnosis and initial management of
acute stroke and transient ischaemic attack (TIA). London: Royal
College of Psychiatrists, 2008.
11. Incalzi RA, Corsonello A, Pedone C, et al. From Global Initiative for
Chronic Obstructive Lung Disease (GOLD) guidelines to current
clinical practice: an overview of the pharmacological therapy of
stable chronic obstructive pulmonary disorder. Drugs Aging
2006;23:411–20.
12. National Collaborating Centre for Mental Health. Depression: the
NICE guideline on the treatment and management of depression in
adults. London: The British Psychological Society and The Royal
College of Psychiatrists, 2010.
13. Uhlig K, Leff B, Kent D, et al. A Framework for crafting clinical
practice guidelines that are relevant to the care and management of
people with multimorbidity. J Gen Intern Med 2014;29:670–9.
14. Veehof LJ, Stewart RE, Myeboom-de Jong B, et al. Adverse drug
reactions and polypharmacy in the elderly in general practice. Eur J
Clin Pharmacol 1999;55:533–6.
15. Rollason V, Vogt N. Reduction of polypharmacy in the elderly: a
systematic review of the role of the pharmacist. Drugs Aging
2003;20:817–22.
16. Gnjidic D, Hlimer SN, Blyth FM, et al. Polypharmacy cutoff and
outcomes: five or more medicines were used to identify
community-dwelling older men at risk of different adverse outcomes.
J Clin Epidemiol 2012;65:989–95.
17. Bushardt RL, Massey EB, Simpson TW, et al. Polypharmacy:
misleading, but manageable. Clin Interv Aging 2008;3:383–9.
18. Munter P, Colanetion LD, Cushman M, et al. Validation of the
atherosclerotic cardiovascular disease pooled cohort risk equations.
JAMA 2014;311:1406–15.
19. Dagenais GR, Lu J, Faxon DP, et al. Prognostic impact of the
presence and absence of angina on mortality and cardiovascular
outcomes in patients with type 2 diabetes and stable coronary artery
disease: results from the BARI 2D (Bypass Angioplasty
Revascularization Investigation 2 Diabetes (DIABETES) trial. 

J Am Coll Cardiol 2013;61:702–11.

20. Hussey PS, Schneider EC, Rudin RS, et al. Continuity and the costs of care for chronic disease. JAMA Intern Med 2014;174:742–8.

21. Buckwalter JA, Saltzman C, Brown T. The impact of osteoarthritis: implications for research. Clin Orthop Relat Res 2004;427(Suppl): S6–15.

22. Judd LL, Schettler PJ, Akiskal HS. The prevalence, clinical relevance, and public health significance of subthreshold depressions. Psychiatr Clin North Am 2002;25:685–98.

23. Porcheret M, Hughes R, Evans D, et al. Data quality of general practice electronic health records: the impact of a program of assessments, feedback, and training. J Am Med 2004;11:78–86.

24. Harding A, Stuart-Buttle C. The development and role of the read codes. J AHIMA 1998;69:34–8.

25. British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary, No. 58 September 2009. London: BMJ Group and Pharmaceutical Press, 2009.

26. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22:363–88.

27. Townsend P, Phillimore P, Beattie A. Health and deprivation: inequality and the north. London: Croom Helm, 1988.

28. Huffman MD, Yusuf S. Polypills: essential medicines for cardiovascular disease secondary prevention? J Am Coll Cardiol 2014;63:1368–70.

29. Greving JP, Dening P, van der Veen WJ, et al. Does comorbidity explain trends in prescribing of newer antihypertensive agents? J Hypertens 2004;22:2209–15.

30. Gill JM, Klinkman MS, Chen YX. Antidepressant medication use for primary care patients with and without medical comorbidities: a national electronic health record (EHR) network study. J Am Board Fam Med 2010;23:499–508.

31. Weidinger P, Nilsson JL, Lindblad U. Adherence to diagnostic guidelines and quality indicators in asthma and COPD in Swedish primary care. Pharmacoepidemiol Drug Saf 2009;18:393–400.

32. Jordan K, Porcheret M, Croft P. Quality of morbidity coding in general practice computerized medical records: a systematic review. Fam Pract 2004;21:396–412.

33. Rushton CA, Strömberg A, Jaarsma T. Multidrug and optimal heart failure therapy prescribing in older general practice populations: a clinical data linkage study. BMJ Open 2014;4:e003698.