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 0.8). 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.[6 7]

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.[8–12] 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.[13] 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.[14–16] 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.[16] This lack of consensus defined approach to this problem has led to an argument for less ambiguous terminology,[17] 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.[18 19] The other three non-vascular chronic conditions—COPD, OA and depression—are leading causes of morbidity, high cost of care and psychological distress, respectively.[20–22] 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 socioeconomic 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.[23]

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).[24] 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 (PiPCA) database focuses on the routinely collected prescribed medications and which were coded using the British National Formulary (BNF) classification.[25] 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 any one of the key group of drugs for COPD, OA or depression. The group of drugs derived from guidelines for COPD[10] included bronchodilators, corticosteroids, inhaled steroids and oxygen (BNF sections 3.1, 3.2, 3.5 and 3.6). The group of drugs for OA[26] 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[11] 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 χ^2 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.[27] 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

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 (χ^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-inflammatories (15% vs 18%; χ^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,[15] our study

Table 1 Prescribed drug prevalence by BNF main chapter and specific sections

BNF chapter	BNF subsections	BNF classification	Drug examples	Number	Drug prevalence/ 10 000†
2 Cardiovascular system				9384	7289
	2.9	Antiplatelet drugs	Aspirin, clopidogrel, dipyridamole	5044	3918
	2.8	Anticoagulants	Warfarin	669	520
	2.2	Diuretics	Thiazide diuretics	4912	3815
	2.4	β-blockers	Bisoprolol	4034	3133
	2.5	ACE inhibitors or ARB	Ramipril, candesartan	4250	3301
	2.6	nitrates, calcium antagonists	GTN, amlodipine	4984	3817
	2.12	Lipid regulating drugs	Simvastatin	4894	3801
3 Respiratory system				2861	2222
	3.1	Bronchodilators	Salbutamol	2775	2155
	3.2	Corticosteroids	Beclomethasone	2140	1662
	3.6	Oxygen	NA	94	73
4 Central nervous system drugs				7478	5808
	4.7.1	Non-opioid analgesics	Paracetamol	5395	4190
	4.7.2	Opioid analgesics	Codeine, tramadol	855	664
	4.1	Hypnotics and anxiolytics	Diazepam	1180	917
	4.3	Selective serotonin reuptake inhibitors Tricyclic antidepressants	Fluoxetine, citalopram, amitriptyline	3241	2517
6 Endocrine system				2916	2265
	6.1.1	Insulin	Insulin, humalog	632	491
	6.1.2	Oral antidiabetic drugs	Metformin, gliclazide	2334	1805
10 Musculoskeletal and joint disease				2143	1664
	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.

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[28] but

Table 2 Sociodemographic characteristics of the main drug categories

| Factor | Total numbers | Main drug categories | | | | |
		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)	1565 (26)	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 of Deprivation, figures in brackets refer to the percentage of each study factor subgroup.

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 3 Associations between individual study groups and higher multidrug counts

| Conditions | Multidrug number/10 000 population | | | | | | Adjusted OR (95% CI) |
	0	1	2	3	4	5	
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	0	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.

Table 4 Associations between vascular comorbidity groups and higher multidrug counts

Conditions	Multidrug number/10 000 population						Adjusted OR (95% CI)
	0	1	2	3	4	5	
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.

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 the overall prescribing of multiple drugs and when the unit of analysis for outcome is not the disease but the arguably more important patient-centred outcomes.

The large scale study of specified chronic diseases was conducted using an anonymised database for a 2-year time period. In terms of the cross-sectional associations, the findings on the levels of chronic conditions, comorbidity and multidrug 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,[32] 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

Table 5 Key drug treatments of non-vascular conditions in vascular comorbidity

Numbers (%)	Key drug treatments*		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
	No	Yes		
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.

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 specific common diagnostic categories. Further research is also required for the arguably more complex assimilation of the range of defined drug categories, other multimorbidity and to investigate specific effect of individual drug categories. Most of these drugs, other than analgesia 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 findings show the links between common chronic conditions, comorbidity and associated multidrug prescribing. The key and distinct finding is that the study shows that multidrug prescribing 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 conditions 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[33] but 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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