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

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**Title: Chronic condition comorbidity and multi-drug therapy in general practice  
populations: a cross-sectional linkage study**

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## Abstract

**Objectives:** The study investigated (i) the association between comorbidity and multi-drug prescribing compared to the index condition, and (ii) the association between vascular comorbidity and non-vascular condition optimal 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) were: (i) six chronic condition groups, (ii) combined vascular group (at least one of diabetes mellitus, cardiovascular disease or cerebrovascular disease) and (iii) non-vascular conditions with chronic obstructive pulmonary disease, osteoarthritis or depression.

**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 multi-drug count as 3 or more. Optimal group of drugs for COPD, OA and depression were derived from guidelines.

**Results:** The adjusted associations between the comorbid groups and higher multi-drug count compared to their respective 'alone' group were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

In COPD, vascular comorbidity was associated with a significant reduction in optimal COPD drug treatment (adjusted Odds Ratio 0.6 (95% confidence interval 0.4 to 0.8)). In depression, vascular comorbidity was associated with a reduction in optimal depression drug treatment (OR 0.6 (0.4 to 0.7)).

**Conclusions:** The study shows that multi-drug prescribing defined by a range of selected but different systems, is higher with comorbidity and may be associated with sub-optimal prescribing. The importance of these findings is whether such multi-drug therapy influences the outcomes of care for chronic conditions.

## Article summary

### *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 multi-drug measurement which accounts for vascular condition-specific drugs as well as summarising non-vascular co-drug therapy.
- The study provides the emergent approach to investigating the influence of multi-drug therapy on 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 multi-drug 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 multi-drug dose and duration on longer-term outcomes.

## Introduction

Comorbidity is defined as other co-occurring diseases in the same individual with an index condition, and is important concept as other conditions may influence the progression and treatment of the index condition.<sup>1</sup> Current evidence of the overall implications of chronic diseases, have shown that this phenomenon is associated with adverse health, increased health care utilisation and increased mortality.<sup>2,3,4</sup> 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 drugs 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.<sup>5,6</sup>

Many national health care 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.<sup>7,8,9,10,11</sup> 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.<sup>12</sup> 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 (i) how does multiple drug prescribing relate to the primary index condition and (ii) how does multiple drug prescribing escalate when populations experience multiple conditions which might be directly linked or occur by chance together. The cardio-metabolic 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 patho-physiology. 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.

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3 In terms of the current evidence in this field, much of it has focused around  
4 'polypharmacy' studies.<sup>13,14,15</sup> However, whilst this might seem an appropriate broad  
5 umbrella term, in research and clinical approaches, it has often focused on multiple drugs  
6 and adverse associated events. Within this evidence, this still creates the gap of how  
7 multiple conditions link to multiple drugs prescribing, and whether comorbidity influences  
8 the optimal prescribing of an index disease.  
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13 In this study, the focus was on six common chronic conditions in the general population,  
14 which included diabetes mellitus, cardiovascular diseases, cerebrovascular diseases  
15 chronic obstructive pulmonary diseases, osteoarthritis and depression. The choice of  
16 these chronic conditions for the purpose of the study is based on a number of factors  
17 including the epidemiology, especially prevalence of the diseases, as well as aetio-  
18 pathogenesis and impacts on quality of life and psychological well-being. For example,  
19 while diabetes mellitus, coronary heart disease and cerebrovascular diseases have a  
20 common pathological basis of causation (the 'vascular group'), and often co-exist in one  
21 patient, they are also known to have high mortality rates - hence the drive towards  
22 measures aimed at optimising the management of these disease.<sup>16,17</sup> The other three,  
23 non-vascular chronic conditions - Chronic Obstructive Pulmonary Disease, Osteoarthritis  
24 and Depression are leading causes of morbidity, high cost of care and psychological  
25 distress respectively.<sup>18,19,20</sup> In addition to investigating the relative multiple drugs  
26 prescribing in comorbidity compared to one of the six index examples, there was also a  
27 test of whether comorbidity influenced optimal drug prescribing.  
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## 40 **Methods**

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42 **Design and Study population:** The cross-sectional study was conducted using two  
43 linked databases on patients aged 40 years and over presenting to general practice over  
44 a 2-year time period (from 1<sup>st</sup> January 2002 to 31<sup>st</sup> December 2003).  
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48 **Settings:** The clinical and prescription databases analysed were derived from an  
49 anonymised computer recorded consultations from eleven general practices from the  
50 North Staffordshire Keele GP research partnership. The partnership covers a range of  
51 practices covering varying socioeconomic groups within rural and urban areas and has  
52 been involved in data collection over time for the purpose of epidemiological studies.  
53 There is an on-going process of data validation to improve data quality, and there is  
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3 evidence that this measure improves data recording by general practitioners and their  
4 teams.<sup>21</sup>  
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7 **Chronic disease data:** The Consultation in Primary Care Archive (CiPCA) database  
8 focuses on the routinely collected morbidity encounters in actual consultations and coded  
9 using a standard clinical classification (Read codes).<sup>22</sup> Patients who had a record of a  
10 disease-specific READ coded morbidity of interest were included in the study and the  
11 main codes were used with all associated “daughter codes”. The main READ codes that  
12 were used to define the chronic disease groups were: diabetes mellitus (Read codes  
13 C10), cardiovascular diseases (ischaemic heart disease (G3); heart failure (G58),  
14 excluding hypertension)), cerebrovascular diseases (G6), chronic obstructive pulmonary  
15 disease (H30, excluding asthma) (COPD), osteoarthritis (N05, excluding arthralgia), and  
16 depression (E11, E20, Eu and excluding psychosis).  
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### 23 **Study groups: definitions**

24 The patients were classified into the individual condition groups, and then two specific  
25 study groups were constructed: vascular group (population with at least one of diabetes  
26 mellitus, cardiovascular disease or cerebrovascular disease) and non-vascular group of  
27 individual conditions (chronic obstructive pulmonary disease, osteoarthritis or depression).  
28 The individual groups enabled the comparison of index groups to those with comorbidity.  
29 The vascular group were likely to be on similar multiple drugs, so a separate hypothesis  
30 was tested, that was prescribing in vascular conditions overall may influence prescribing  
31 in the individual non-vascular conditions of chronic obstructive pulmonary disease,  
32 osteoarthritis and depression.  
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### 40 **Comorbidity: definitions**

41 There were two approaches to defining comorbidity. First, comorbidity was defined as the  
42 presence of one of the other five selected conditions. So using the diabetes population as  
43 an example, the diabetes ‘index’ group was defined as diabetes ‘alone’ and without  
44 anyone of the other five conditions, whereas diabetes ‘comorbid’ group was defined as at  
45 least one of the other five conditions. This definition was applied to each of the six chronic  
46 conditions individually. Second, in the vascular group, comorbidity was defined separately  
47 as the individual and specific addition of COPD, OA or depression, and irrespective of  
48 whether the latter three occurred together.  
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3 The approach taken to looking at specific groups and conditions was based on a  
4 combination of clinical rationale and feasibility. Whilst, one could have investigated any  
5 number of combinations of the six conditions, the better and preferred approach taken  
6 was to group conditions first at the “Vascular” level. As highlighted earlier, diabetes,  
7 ischaemic heart disease and cerebrovascular disease have shared pathogenesis and  
8 there may be over-lapping of drug treatments. However, the “non-vascular” group  
9 constitute individual chronic conditions with distinct and un-related drug treatments. This  
10 approach enabled comorbidity definitions based on (i) group-level i.e. vascular  
11 comorbidity with one of the non-vascular conditions and (ii) counts i.e. number of other  
12 conditions for each of the six index groups.  
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### 19 **Prescribed drug measure: overall multi-drug count definitions**

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22 The Prescriptions in Primary Care Archive (PiPCA) database focuses on the routinely  
23 collected prescribed medications and which were coded using the British National  
24 Formulary (BNF) classification.<sup>23</sup> The BNF consists of 15 main chapters based on the  
25 systems of the body, and within which there are further sub-sections for specific clinical  
26 indications. Only patients on repeat drug prescriptions were selected for defining  
27 measures because this gives a better representation of multiple drugs used on a long  
28 term basis for the majority of patients with chronic conditions.  
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34 Specific drug treatment chapters for the six chronic diseases of interest in the study were  
35 identified and used as a summary of multi-drug counts. The BNF chapter for  
36 cardiovascular and cerebrovascular drugs were under BNF chapter 2, for COPD drugs  
37 under chapter 3, for depression under chapter 4, for diabetes mellitus under chapter 6,  
38 and for osteoarthritis under chapters 4 and 10. This means that overall; there were five  
39 main BNF chapters, which could constitute a measure of drug counts of up to a total of 5.  
40 The multi-drug count definition in this approach would specifically relate to people  
41 prescribed drugs from at least two or more of the five chapters indicated.  
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### 47 **Prescribed drug measure: optimal drug definitions**

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50 Optimal drug treatment for the specific conditions of COPD, OA and depression was also  
51 investigated. Whilst optimal drug treatment of these conditions can be examined in  
52 different ways such as the use of specific drugs, or drug doses and duration of drug  
53 therapy, we wanted to first establish the simplest likelihood of a patient given an optimal  
54 group of drugs for COPD, OA or depression. The optimal group of drugs derived from  
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3 guidelines for COPD<sup>10</sup> included bronchodilators, corticosteroids, inhaled steroids,  
4 mucolytics (BNF sections 3.1, 3.2, 3.5 and 3.6). The optimal group of drugs for  
5 osteoarthritis<sup>24</sup> included non-opioid analgesics, opioid analgesics, non-steroidal anti-  
6 inflammatories, and Cox 2 inhibitors (BNF sections 4.7.1, 4.7.2, 10.1.1 and 10.1.2.2). The  
7 optimal group of drugs for depression<sup>11</sup> included hypnotics, anxiolytics and  
8 antidepressants (BNF sections 4.1 and 4.3).

### 13 Analysis

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16 The first analyses was to describe the 2-year period prevalence of the 5 main BNF  
17 chapters in the specified chronic disease population, with a focus on some of the common  
18 drugs that were prescribed within each chapter expressed as drug prevalence/10,000  
19 population aged 40 years and over. The five main chapter drug categories prevalence are  
20 described by age, gender and deprivation status. Deprivation was measured by the Index  
21 of Multiple Deprivation (IMD) which is a composite score that is linked to postal address  
22 codes.<sup>25</sup> The IMD score was categorised into the bottom 20% (most deprived), middle  
23 60% and the top 20% score (most affluent).

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26 For each of the six chronic conditions, associations between the comorbid groups and  
27 higher multi-drug counts were compared to the respective reference 'alone' group. The  
28 'outcome' of higher multi-drug therapy was defined as 3 or more of the chapter counts and  
29 compared to 2 counts or less. Associations were expressed as Odds Ratios (OR) with  
30 95% confidence intervals (CI), and also included the ratios comparing prevalence of each  
31 drug count category in the comorbid group compared to the 'alone' group. Then for the  
32 vascular group, associations between each of the comorbid group with COPD, OA or  
33 depression were compared to the vascular 'alone' alone and higher multi-drug counts  
34 were then estimated.

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37 Finally, the data was analysed for the study defined optimal drug treatments for COPD,  
38 OA or depression. Three study groups constructed were: COPD and at least one of the  
39 vascular conditions; OA with at least one of the vascular conditions; and depression with  
40 at least one of the vascular conditions. Each group was the compared to their respective  
41 vascular group e.g. COPD and vascular group compared to COPD without a vascular  
42 condition, by the specific optimal drug treatment. Association estimates are presented  
43 both as unadjusted and adjusted figures with 95% confidence intervals. Analyses were  
44 carried out using SPSS version 17.0 statistical software.

## Results

### Study population

In the study population of 12,875 aged 40 years and over, the 2-year time-period prevalence estimated per 10,000 for the cardiovascular system drugs was 7,289, for respiratory system drugs was 2,222, for non-opioid analgesia was 4,190, for anti-depressants was 2,517, for anti-diabetic drugs was 2,265 and musculoskeletal system anti-inflammatory drugs was 1,664 (**Table 1**).

In terms of the socio-demographic distribution, older patients aged 70 years and over and populations in the top 20% deprivation status were more likely to be prescribed all five main drug categories. For women compared to men, there was variation by type of main drug category; the comparative 2-year prevalence figures by gender were higher for men compared to women for the cardiovascular system drugs (76% vs 70%) and diabetes (26% vs 20%), but similar for COPD. Prevalence figures were lower for men compared to women for anxiolytics and anti-depressants (49% vs 66%) and anti-inflammatories (15% vs 18%) (**Table 2**).

### Individual chronic condition comorbidity and higher multi-drug 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 to 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 multi-drug count of 4, and these ranged from 13.7 for the depression comorbid group to 2.3 for diabetes comorbid group.

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

### Vascular condition comorbidity and higher multi-drug counts

The prevalence ratios for the multi-drug count of 5 ranged from 3.9 for vascular group comorbid with osteoarthritis, 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 multi-group count compared to their respective 'alone' group ordered by strength of association were: Odds ratio 4.6 (95% Confidence Intervals 3.8 to 5.7) for vascular group comorbid with COPD, OR 3.2 (2.6 to 3.9) for vascular group comorbid with depression, and vascular group comorbid with OA OR 3.0 (2.6 to 3.5).

### 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 to their respective group without vascular conditions showed a significant reduction in optimal COPD drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.8). Adjusting for age, gender and deprivation, the association between the depression and vascular comorbid groups compared to their respective group without vascular conditions showed a significant reduction in optimal depression drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.7). Adjusting for age, gender and deprivation, the association between the OA and vascular comorbid groups compared to their respective group without vascular conditions did not show a statistically significant reduction in optimal OA drug treatment with an Odds Ratio of 0.8 (95% confidence interval 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 multi-drug prescribing, which was higher in the presence of comorbidity compared to the respective index groups. Whilst previous evidence has shown the high levels of 'polypharmacy'<sup>15</sup>, our study findings link the disease status, comorbidity status to the measure of multi-drug prescribing. Depending on whether the chronic conditions were vascular (diabetes, cardiovascular or cerebrovascular) or the non-vascular (COPD, OA or depression), the higher levels of multi-drug prescribing varied. All six conditions with comorbidity compared to their index condition had much higher multi-drug count, even

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3 adjusting for age, gender and deprivation. The measure of multi-drug count was notably  
4 distinct by the use of five different main drug chapter categories which were for different  
5 body systems, which means that this 'outcome' was not about multiple drugs use for the  
6 same condition. For example, a diabetic with a higher multi-drug count of 4 or 5 in this  
7 study relates to different and distinct body systems, and not to the different drugs under  
8 the same chapter. The chronic condition of depression comorbidity had the strongest  
9 strength of association with higher multi-drug counts, followed by cardiovascular disease  
10 comorbidity, and the estimates of association for cerebrovascular disease, osteoarthritis  
11 and diabetes were similar. These findings suggest that the index condition and  
12 comorbidity may influence the range of multi-drug prescribing, and generates the  
13 interesting hypothesis on the potential variation in clinical outcomes of the index  
14 conditions may be because of underlying comorbid drug prescribing.

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16 The study also grouped the vascular-related conditions to investigate the influence of non-  
17 vascular drug prescribing compared to vascular conditions 'alone' (i.e. without any one of  
18 COPD, OA or depression). Again, the adjusted associations were significant, with  
19 vascular comorbidity being associated with higher-multi-drug counts compared to the  
20 respective 'vascular index' group. Here the clinical implication is that vascular comorbidity  
21 in populations aged 40 years and over might not only be associated with multiple vascular  
22 drugs as routinely suggested by clinical guidelines<sup>26</sup>, but by a range of conditions such as  
23 comorbidity of COPD, OA or depression. It is possible that these conditions and the drug  
24 treatments for them may also in the end influence the health and healthcare outcomes of  
25 the index vascular conditions.<sup>27</sup>

26  
27 In terms of the influence of comorbidity on optimal drug prescribing, our study findings  
28 show that vascular comorbidity in COPD and depression is associated with sub-optimal  
29 drug prescribing for the respective conditions of COPD and depression. Similar findings,  
30 particularly for sub-optimal depression drug treatment, when depression is comorbid with  
31 chronic disease has been shown previously.<sup>28,29</sup> However, such findings for osteoarthritis  
32 were not found, and here it is possible that the 'outcome' of analgesia was too broad, as  
33 analgesia use covers a range of other painful conditions, in addition to osteoarthritis.

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35 Although the optimal drug definition was simple and broad, our study findings seem to  
36 suggest that comorbidity does influence optimal drug prescribing, and further reasons for  
37 this might dis-entangle whether it is due to drug therapeutic or diagnostic conflicts.

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39 The large scale study of specified chronic diseases was conducted using an anonymised  
40 database for a 2-year time-period. In terms of the cross-sectional associations, the  
41 findings on the levels of chronic conditions, comorbidity and multi-drug prescribing do offer  
42 clinical implications as outlined earlier. However, the implications of the associations

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3 between comorbidity and optimal drug definitions may be limited in this cross-sectional  
4 design and these may be treated cautiously as emergent findings. The chronic disease  
5 definitions were also based on routinely collected registers from general practices, which  
6 were and are part of a research network dedicated to the collection of clinical data in  
7 actual consultation. Whilst these chronic disease registers may be subject to variations in  
8 recording<sup>30</sup>, the study analyses provide the estimates of association in actual clinical  
9 practice across 11 different sites. The drug definitions were based on routinely coded  
10 repeat prescriptions and over a 2-year time-period represent an appropriate measure at  
11 the broad system category. Most of these drugs, other than analgesia such as anti-  
12 inflammatories, are not available over the counter and are usually clinician prescribed. So  
13 it is possible that common over the counter drugs, particularly in relation to osteoarthritis,  
14 may be an under-estimate; however, the selection of repeated prescribing would mitigate  
15 against such under-estimation. Finally, although a large scale study, these general  
16 practices are drawn from one region of England, and whilst this might limit generalisability,  
17 the internal validity of the findings still remains.

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19 In conclusion, our study findings show the links between common chronic conditions,  
20 comorbidity and associated multi-drug prescribing. The key and distinct finding is that the  
21 study shows that multi-drug prescribing defined by a range of selected but different  
22 systems is high in chronic conditions and higher in comorbidity. The common group of  
23 vascular conditions are not the only ones associated with their 'own' guideline driven  
24 multi-drug therapy, but the addition of non-vascular conditions such as COPD, OA and  
25 depression adds to the multi-drugs burden in patients. The importance of these findings,  
26 in addition to quantifying the scale, is whether such multi-drug therapy influences the  
27 quality of care for each of the individual conditions. Our findings suggest the potential for  
28 sub-optimal drug treatment as a consequence in line with other evidence<sup>31</sup>, but further  
29 research is required to investigate the impact of disease status, comorbidity, multi-drug  
30 therapy on prospective and long-term outcomes of clinical care.  
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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 <sup>†</sup>
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	Beta 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
	3.5	Respiratory stimulants	Doxapram	0	0
	3.6	Oxygen		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 anti-diabetic 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

<sup>†</sup>Population refers to those with one of six chronic conditions ( $n = 12875$ ), which included hypertension, diabetes, coronary heart disease, cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD), osteoarthritis (OA) and depression; Drug categories are based on the British National Formulary (BNF)

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**Table 2: Socio-demographic characteristics of the main drug categories**

Factor	Total Numbers	Main drug categories				Musculo-skeletal System <sup>4</sup>
		Cardiovascular system	Respiratory System <sup>1</sup>	Central-nervous System <sup>2</sup>	Endocrine System <sup>3</sup>	
<b>Age (years)</b>						
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 years and over	715	608 (85)	135 (19)	513 (72)	101 (14)	59 (8)
<b>Gender</b>						
Women	6896	4813 (70)	1510 (22)	4528 (66)	1351 (20)	1260 (18)
Men	5979	4571 (76)	1351 (23)	2950 (49)	1565 (26)	883 (15)
<b>Deprivation**</b>						
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 sub-group*



Table 3: Associations between individual study groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (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 (3.0-4.2)
<i>Prevalence ratio</i>	<i>0.2</i>	<i>0.4</i>	<i>0.5</i>	<i>1.5</i>	<i>2.3</i>	<i>3.3</i>	
CHD 'alone'	148	4057	4248	1372	160	16	1.0
CHD comorbidity	36	1027	3973	3516	1327	121	5.35 (4.6-6.3)
<i>Prevalence ratio</i>	<i>0.2</i>	<i>0.3</i>	<i>0.9</i>	<i>2.6</i>	<i>8.3</i>	<i>7.6</i>	
CVD 'alone'	688	4087	3848	1306	70	0	1.0
CVD comorbidity	41	1745	4251	3224	678	62	3.70 (2.8-5.0)
<i>Prevalence ratio</i>	<i>0.1</i>	<i>0.4</i>	<i>1.1</i>	<i>2.5</i>	<i>9.7</i>	<i>n/a</i>	
COPD 'alone'	940	2487	3496	2726	350	0	1.0
COPD comorbidity	189	946	2855	4117	1751	142	3.22 (2.6-4.0)
<i>Prevalence ratio</i>	<i>0.20</i>	<i>0.4</i>	<i>0.8</i>	<i>1.5</i>	<i>5.00</i>	<i>n/a</i>	
OA 'alone'	1378	2786	3722	1854	256	5	1.0
OA comorbidity	174	1260	3550	3420	1325	271	3.64 (3.1-4.3)
<i>Prevalence ratio</i>	<i>0.1</i>	<i>0.5</i>	<i>1.0</i>	<i>1.8</i>	<i>5.2</i>	<i>54</i>	
Depression 'alone'	1912	4140	3093	776	79	0	1.0
Depression comorbidity	325	1422	3555	3555	1082	62	7.11 (5.6-9.0)
<i>Prevalence ratio</i>	<i>0.17</i>	<i>0.34</i>	<i>1.15</i>	<i>4.58</i>	<i>13.7</i>	<i>n/a</i>	

\*Alone – people with disease alone and none of the other 5 morbidities, comorbidity is 1 or more of other 5 study morbidities, \*\*Comorbid drug 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 to 4 combined) compared to lower drug counts (2 or less), CHD is coronary heart disease and CVD is cerebro-vascular disease

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**Table 4: Associations between vascular comorbidity groups and higher multi-drug counts**

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (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 (3.8-5.7)
<i>Prevalence ratio</i>	<i>0.43</i>	<i>0.29</i>	<i>0.71</i>	<i>1.65</i>	<i>2.60</i>	<i>1.90</i>	
Vascular group and OA	29	873	3493	3697	1557	349	3.01 (2.6-3.5)
<i>Prevalence ratio</i>	<i>0.15</i>	<i>0.37</i>	<i>0.87</i>	<i>1.45</i>	<i>2.01</i>	<i>3.92</i>	
Vascular group and Depression	69	829	3733	3917	1359	92	3.22 (2.6-3.9)
<i>Prevalence ratio</i>	<i>0.35</i>	<i>0.35</i>	<i>0.93</i>	<i>1.54</i>	<i>1.76</i>	<i>1.03</i>	

\*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 to 4 combined) compared to lower drug counts (2 or less)

**Table 5: Optimal drug treatment of non-vascular conditions in vascular comorbidity**

Numbers (%)	Optimal drug treatment		Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (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 (0.43-0.78)	0.55 (0.40-0.75)
OA without vascular comorbidity	281 (16)	1440 (84)	1.0	1.0
OA and vascular comorbidity	117 (17)	568 (83)	0.95 (0.75-1.20)	0.82 (0.64-1.06)
Depression without vascular comorbidity	259 (16)	1378 (84)	1.0	1.0
Depression and vascular group	120 (28)	311 (72)	0.49 (0.38-0.62)	0.55 (0.42-0.73)

*\*\*Optimal drug treatment for COPD, OA or depression respectively, adjusted for age, gender and deprivation as measured by Index of Multiple deprivation*

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**Contributorship Statement**

ER and DG coordinated the study data collection and contributed to the writing of the manuscript. ER, DG 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

**Competing Interests**

None

**Data sharing statement**

Data is not available for sharing under existing governance arrangements.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
<b>Methods</b>			
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) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
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	5-7
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	n/a
<b>Results</b>			

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	8
		(b) Give reasons for non-participation at each stage	n/a
		(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	8
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers of outcome events or summary measures	8-9
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	8-9
		(b) Report category boundaries when continuous variables were categorized	n/a
		(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	n/a
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	9-10
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	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
<b>Other information</b>			
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	11

\*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](http://www.strobe-statement.org).

# BMJ Open

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

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**Title: Chronic condition comorbidity and multi-drug therapy in general practice  
populations: a cross-sectional linkage study**

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*Key words: co-morbidity; drug therapy; chronic disease; depression; epidemiology*

*Main text count: 3870*

### Abstract

**Objectives:** The study investigated (i) the association between comorbidity and multi-drug prescribing compared to the index condition, and (ii) the association between vascular comorbidity and non-vascular condition optimal 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 5 conditions was compared to an 'alone' group without them. Additionally how the 'vascular' (one of diabetes, cardiovascular disease and cerebrovascular disease) comorbidity influenced COPD, 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 multi-drug 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 multi-drug count compared to their respective 'alone' group were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

In COPD, vascular comorbidity was associated with a significant reduction in key COPD drug treatments (adjusted Odds Ratio 0.6 (95% confidence interval 0.4 to 0.8). In depression, vascular comorbidity was associated with a reduction in key depression drug treatments (OR 0.6 (0.4 to 0.7)).

**Conclusions:** Our findings show multi-drug 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 multi-drug prescribing influences the outcomes of care for chronic conditions.

## Article summary

### *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 multi-drug measurement which accounts for vascular condition-specific drugs as well as summarising non-vascular co-drug therapy.
- The study provides the emergent approach to investigating the influence of multi-drug 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 multi-drug 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 multi-drug 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.<sup>1,2</sup> 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, have shown that this phenomenon is associated with adverse health, increased health care utilisation and increased mortality.<sup>3,4,5</sup> 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.<sup>6,7</sup>

Many national health care 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.<sup>8,9,10,11,12</sup> 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.<sup>13</sup> 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 (i) how does multiple drug prescribing for different systems relate to the primary index condition and (ii) how does multiple drug prescribing escalate when populations experience multiple conditions which might be directly linked or occur by chance together. The cardio-metabolic 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 patho-physiology. For example, other common chronic conditions include chronic obstructive airways disease and

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3 depression, and this epidemiology provides the scale of multiple drug therapies when co-  
4 occurring conditions might be un-related.  
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7 In terms of the current evidence in this field, much of it has focused around  
8 'polypharmacy' studies.<sup>14,15,16</sup> However, whilst this might seem an appropriate broad  
9 umbrella term, in research and clinical approaches, it has often focused on arbitrarily  
10 chosen number of drugs, and linked the term to either inappropriate prescribing or  
11 associated adverse events in older populations.<sup>16</sup> This lack of consensus defined  
12 approach to this problem has led to an argument for less ambiguous terminology<sup>17</sup>, and  
13 we propose that 'multi-drug' therapy is used to link in with the standard approach to two or  
14 more conditions, which is 'multi-morbidity'. Within this evidence, there is still a clear gap in  
15 how morbidity link to drug prescribing, and whether comorbidity influences the drug  
16 prescribing for an index disease.  
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23 In this study, the focus was on six common chronic conditions in the general population,  
24 which included diabetes mellitus, cardiovascular diseases, cerebrovascular diseases  
25 chronic obstructive pulmonary diseases, osteoarthritis and depression. The choice of  
26 these chronic conditions for the purpose of the study was based on a number of factors  
27 including the epidemiology, especially prevalence of the diseases, as well as aetio-  
28 pathogenesis and impacts on quality of life and psychological well-being. For example,  
29 while diabetes mellitus, coronary heart disease and cerebrovascular diseases have a  
30 common pathological basis of causation (the 'vascular group'), and often co-exist in one  
31 patient, they are also known to have high mortality rates - hence the drive towards  
32 measures aimed at optimising the management of these diseases.<sup>18,19</sup> The other three,  
33 non-vascular chronic conditions - chronic obstructive pulmonary disease (COPD),  
34 osteoarthritis (OA) and depression are leading causes of morbidity, high cost of care and  
35 psychological distress respectively.<sup>20,21,22</sup> The rationale for our focus on few selected  
36 common conditions was also to provide common comorbidity combinations which are  
37 potentially treated with drugs as a key intervention.  
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47 We investigated two separate issues using the selected group of vascular and non-  
48 vascular conditions. First, we wanted to investigate the relative multi-drug prescribing for  
49 each of six chosen index examples, comparing comorbid groups with prescribing levels in  
50 the respective index groups. Second, we wanted to test of whether vascular comorbidity  
51 influenced key drug prescribing for chosen conditions. The vascular group were likely to  
52 be on similar multiple drugs, so the distinct hypothesis was tested, that was drug  
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3 prescribing in vascular conditions overall may influence key drug prescribing in the  
4 individual non-vascular conditions of COPD, OA or depression.  
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## 7 **Methods**

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10 **Design and Study population:** The cross-sectional study was conducted using two  
11 linked databases on patients aged 40 years and over presenting to general practice over  
12 a 2-year time period (from 1<sup>st</sup> January 2002 to 31<sup>st</sup> December 2003). We wanted to  
13 investigate what multi-drug prescribing levels were before a national UK performance-  
14 based incentive (Quality outcomes Framework) was implemented to test the associations  
15 between comorbidity and routine multi-drug prescribing. Ethical approval for the use of  
16 these anonymised databases was granted by the North Staffordshire Research Ethics  
17 Committee  
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23 **Settings:** The clinical and prescription databases analysed were derived from an  
24 anonymised computer recorded consultations from eleven general practices from the  
25 North Staffordshire Keele GP research partnership. The partnership covers a range of  
26 practices covering varying socioeconomic groups within rural and urban areas and has  
27 been involved in data collection over time for the purpose of epidemiological studies.  
28 There is an on-going process of data validation to improve data quality, and there is  
29 evidence that this measure improves data recording by general practitioners and their  
30 teams.<sup>23</sup>  
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36 **Chronic disease data:** The Consultation in Primary Care Archive (CiPCA) database  
37 focuses on the routinely collected morbidity encounters in actual consultations and coded  
38 using a standard clinical classification (Read codes).<sup>24</sup> Patients who had a record of a  
39 disease-specific READ coded morbidity of interest were included in the study and the  
40 main codes were used with all associated “daughter codes”. The main READ codes that  
41 were used to define the chronic disease groups were: diabetes mellitus (Read codes  
42 C10), cardiovascular diseases (ischaemic heart disease (G3); heart failure (G58),  
43 excluding hypertension)), cerebrovascular diseases (G6), chronic obstructive pulmonary  
44 disease (H30, excluding asthma) (COPD), osteoarthritis (N05, excluding arthralgia), and  
45 depression (E11, E20, Eu and excluding psychosis).  
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## 53 **Comorbidity: definitions**

54 There were two approaches to defining comorbidity. First, comorbidity was defined as the  
55 presence of one of the other five selected conditions. So using the diabetes population as  
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3 an example, the diabetes 'index' group was defined as diabetes 'alone' and without  
4 anyone of the other five conditions, whereas diabetes 'comorbid' group was defined as at  
5 least one of the other five conditions. The index 'alone' group would also enable the  
6 capture of the other morbidity that was outside of the study selected conditions. This  
7 definition was applied to each of the six chronic conditions individually. Second, in the  
8 vascular group, comorbidity was defined separately as the individual and specific addition  
9 of COPD, OA or depression, and irrespective of whether the latter three occurred  
10 together.  
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### 16 17 **Prescribed drug measure: overall multi-drug count definitions**

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19 The Prescriptions in Primary Care Archive (PiPCA) database focuses on the routinely  
20 collected prescribed medications and which were coded using the British National  
21 Formulary (BNF) classification.<sup>25</sup> The BNF consists of 15 main chapters based on the  
22 systems of the body, and within which there are further sub-sections for specific clinical  
23 indications. Only patients on repeat drug prescriptions were selected for defining  
24 measures because this gives a better representation of multiple drugs used on a long  
25 term basis for the majority of patients with chronic conditions.  
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31 Specific drug treatment chapters for the six chronic diseases of interest in the study were  
32 identified and used as a summary of multi-drug counts. The BNF chapter for  
33 cardiovascular and cerebrovascular drugs were under BNF chapter 2, for COPD drugs  
34 under chapter 3, for depression under chapter 4, for diabetes mellitus under chapter 6,  
35 and for osteoarthritis under chapters 4 and 10. This means that overall; there were five  
36 main BNF chapters, which could constitute a measure of drug counts of up to a total of 5.  
37 The multi-drug count definition in this approach would then specifically relate to people  
38 prescribed drugs from at least two or more of the five chapters indicated.  
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### 45 46 **Vascular comorbidity and drug prescribing for non-vascular conditions**

47 The key likelihood of receiving drug treatments for the specific conditions of COPD, OA  
48 and depression in the study population with vascular comorbidity was also investigated. In  
49 this approach the 'vascular' comorbidity was defined as the group any one of diabetes,  
50 cardiovascular disease and cerebrovascular disease. The non-vascular groups were then  
51 individually compared with and without vascular comorbidity. For example, the COPD  
52 group was compared with vascular comorbidity to the COPD without vascular comorbidity,  
53 in relation to the likelihood of receiving COPD-specific drug treatment.  
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3 Whilst the key drug treatments for COPD, OA and depression can be examined in  
4 different ways such as the use of specific drugs, or drug doses and duration of drug  
5 therapy, we wanted to first establish the simplest likelihood of a patient given any one of  
6 the key group of drugs for COPD, OA or depression. The group of drugs derived from  
7 guidelines for COPD<sup>10</sup> included bronchodilators, corticosteroids, inhaled steroids and  
8 oxygen(BNF sections 3.1, 3.2, 3.5 and 3.6). The group of drugs for osteoarthritis<sup>26</sup>  
9 included non-opioid analgesics, opioid analgesics, non-steroidal anti-inflammatories, and  
10 Cox 2 inhibitors (BNF sections 4.7.1, 4.7.2, 10.1.1 and 10.1.2.2). The group of drugs for  
11 depression<sup>11</sup> included hypnotics, anxiolytics and antidepressants (BNF sections 4.1 and  
12 4.3).

### 19 Analysis

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22 The first analyses was to describe the 2-year period prevalence of the 5 main BNF  
23 chapters in the specified chronic disease population, with a focus on some of the common  
24 drugs that were prescribed within each chapter expressed as drug prevalence/10,000  
25 population aged 40 years and over, and differences were assessed using Chi-square  
26 tests. The five main chapter drug categories prevalence are described by age, gender and  
27 deprivation status. Deprivation was measured by the Index of Multiple Deprivation (IMD)  
28 which is a composite score that is linked to postal address codes.<sup>27</sup> The IMD score was  
29 categorised into the bottom 20% (most deprived), middle 60% and the top 20% score  
30 (most affluent).

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33 For each of the six chronic conditions, associations between the comorbid groups and  
34 higher multi-drug counts were compared to the respective reference 'alone' group. The  
35 'outcome' of higher multi-drug therapy was defined as 3 or more of the chapter counts and  
36 compared to 2 counts or less. Associations using logistic regression were expressed as  
37 Odds Ratios (OR) with 95% confidence intervals (CI), and also included the ratios  
38 comparing prevalence of each drug count category in the comorbid group compared to  
39 the 'alone' group. Then for the vascular group, associations between each of the comorbid  
40 group with COPD, OA or depression were compared to the vascular 'alone' alone and  
41 higher multi-drug counts were then estimated.

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44 Finally, the data was analysed for the study defined optimal drug treatments for COPD,  
45 OA or depression. Three study groups constructed were: COPD and at least one of the  
46 vascular conditions; OA with at least one of the vascular conditions; and depression with  
47 at least one of the vascular conditions. Each group was the compared to their respective

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3 vascular group e.g. COPD and vascular group compared to COPD without a vascular  
4 condition, by the specific optimal drug treatment. Association estimates using logistic  
5 regression are presented both as unadjusted and adjusted figures with 95% confidence  
6 intervals. Analyses were carried out using SPSS version 17.0 statistical software.  
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## 10 Results

### 11 Study population

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15 In the study population of 12,875 aged 40 years and over, the number of patients  
16 prescribed with cardiovascular system drugs were 9,384 (2-year time-period prevalence  
17 73%), respiratory system drugs were 2,861 (22%), non-opioid analgesia were 5,395  
18 (42%), anti-depressants were 3,241 (25%), anti-diabetic drugs were 2,916 (23%) and  
19 musculoskeletal system anti-inflammatory drugs were 2143 (17%) (**Table 1**).  
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24 In terms of the socio-demographic distribution, older patients aged 70 years and over and  
25 populations in the top 20% deprivation status were significantly more likely to be  
26 prescribed all main drug categories, except for the cardiovascular system (Chi-square test  
27 for trend  $p < 0.001$ ). For women compared to men, there was variation by type of main drug  
28 category; the comparative 2-year prevalence figures by gender were significantly higher  
29 for men compared to women for the cardiovascular system drugs (76% vs 70%) and  
30 diabetes (26% vs 20%), but similar for COPD ( $p = 0.462$ ). Prevalence figures were lower  
31 for men compared to women for anxiolytics and anti-depressants (49% vs 66%) and anti-  
32 inflammatories (15% vs 18%) (Chi square test  $p < 0.001$  (**Table 2**)).  
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### 39 Individual chronic condition comorbidity and higher multi-drug counts

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42 For all six specified chronic conditions, at lower drugs counts of up to 2, the prevalence  
43 numbers were greater for the individual groups without the other five comorbid conditions  
44 compared to the numbers for the individual conditions with comorbidity of other five  
45 conditions (**Table 3**). For the drug count of 2 different chapters, the comorbid to 'alone'  
46 ratios ranged from 1.15 for the depression group to 0.5 for the diabetes group. The  
47 prevalence ratios were highest for the multi-drug count of 4, and these ranged from 13.7  
48 for the depression comorbid group to 2.3 for diabetes comorbid group.  
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53 Adjusting for age, gender and deprivation, the associations between the comorbid groups  
54 and higher multi-group count compared to their respective 'alone' group ordered by  
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3 strength of association were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for  
4 depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for  
5 cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for  
6 diabetes, and OR 3.2 (2.6 to 4.0) for COPD.  
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### 10 **Vascular condition comorbidity and higher multi-drug counts**

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12 The prevalence ratios for the multi-drug count of 5 ranged from 3.9 for vascular group  
13 comorbid with osteoarthritis, to 1.9 for vascular group comorbid with COPD, and 1.0 for  
14 the vascular group comorbid with depression (**Table 4**). Adjusting for age, gender and  
15 deprivation, the associations between the comorbid groups and higher multi-group count  
16 compared to their respective 'alone' group ordered by strength of association were: Odds  
17 ratio 4.6 (95% Confidence Intervals 3.8 to 5.7) for vascular group comorbid with COPD,  
18 OR 3.2 (2.6 to 3.9) for vascular group comorbid with depression, and vascular group  
19 comorbid with OA OR 3.0 (2.6 to 3.5).  
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### 26 **Comorbid vascular conditions and optimal non-vascular condition prescribing**

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28 The three specific non-vascular groups of COPD, OA and depression were compared with  
29 comorbid vascular conditions to without such vascular comorbidity in terms of their  
30 respective optimal drug treatment (**Table 5**). Adjusting for age, gender and deprivation,  
31 the association between the COPD and vascular comorbid groups compared to their  
32 respective group without vascular conditions showed a significant reduction in optimal  
33 COPD drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.8).  
34 Adjusting for age, gender and deprivation, the association between the depression and  
35 vascular comorbid groups compared to their respective group without vascular conditions  
36 showed a significant reduction in optimal depression drug treatment with an Odds Ratio of  
37 0.6 (95% confidence interval 0.4 to 0.7). Adjusting for age, gender and deprivation, the  
38 association between the OA and vascular comorbid groups compared to their respective  
39 group without vascular conditions did not show a statistically significant reduction in  
40 optimal OA drug treatment with an Odds Ratio of 0.8 (95% confidence interval 0.6 to 1.1).  
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### 49 **Discussion**

50 Our findings from a large cross-sectional study of nearly 13,000 patients aged 40 years  
51 and over with one of six specified and common chronic conditions showed the scale of  
52 multi-drug prescribing, which was higher in the presence of comorbidity compared to the  
53 respective index groups. Whilst previous evidence has shown the high levels of multiple  
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3 drug prescribing<sup>15</sup>, our study findings link the disease status, comorbidity status to the  
4 measure of multi-drug prescribing for different systems.

5  
6 Depending on whether the chronic conditions were vascular (diabetes, cardiovascular or  
7 cerebrovascular) or the non-vascular (COPD, OA or depression), the higher levels of  
8 multi-drug prescribing varied. All six conditions with comorbidity compared to their index  
9 condition had much higher multi-drug count, even adjusting for age, gender and  
10 deprivation. The measure of multi-drug count was notably distinct by the use of five  
11 different main drug chapter categories which were for different body systems, which  
12 means that this 'outcome' was not about multiple drugs use for the same condition. For  
13 example, a diabetic with a higher multi-drug count of 4 or 5 in this study relates to different  
14 and distinct body systems, and not to the different drugs under the same chapter. The  
15 chronic condition of depression comorbidity had the strongest strength of association with  
16 higher multi-drug counts, followed by cardiovascular disease comorbidity, and the  
17 estimates of association for cerebrovascular disease, osteoarthritis and diabetes were  
18 similar. These findings suggest that the index condition and comorbidity may influence the  
19 range of multi-drug prescribing, and generates the interesting hypothesis on the potential  
20 variation in clinical outcomes of the index conditions may be because of underlying  
21 comorbid drug prescribing.

22  
23 The study also grouped the vascular-related conditions to investigate the influence of non-  
24 vascular drug prescribing compared to vascular conditions 'alone' (i.e. without any one of  
25 COPD, OA or depression). Again, the adjusted associations were significant, with  
26 vascular comorbidity being associated with higher-multi-drug counts compared to the  
27 respective 'vascular index' group. Here the clinical implication is that vascular comorbidity  
28 in populations aged 40 years and over might not only be associated with multiple vascular  
29 drugs as routinely suggested by clinical guidelines<sup>28</sup>, but by a range of conditions such as  
30 comorbidity of COPD, OA or depression. It is possible that these conditions and the drug  
31 treatments for them may also in the end influence the health and healthcare outcomes of  
32 the index vascular conditions.<sup>29</sup>

33  
34 In terms of the influence of comorbidity on key drug prescribing, our study findings show  
35 that vascular comorbidity in COPD and depression is associated with lower likelihood of  
36 drug prescribing for the respective conditions of COPD and depression. Similar findings,  
37 particularly for sub-optimal depression drug treatment, when depression is comorbid with  
38 chronic disease has been shown previously.<sup>30,31</sup> However, such findings for osteoarthritis  
39 were not found, and here it is possible that the 'outcome' of analgesia was too broad, as  
40 analgesia use covers a range of other painful conditions, in addition to osteoarthritis.

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42 Although the key drug definition was simple and broad, our study findings seem to

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3 suggest that comorbidity does influence drug prescribing for specific conditions. Whether  
4 this is due to some kind of therapeutic inertia or is due to GPs' reasoned consideration of  
5 drug-drug and drug-disease interactions and the overall well-being of the patient is the  
6 important question raised by the findings.  
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11 The approach taken to looking at specific groups and six common conditions was based  
12 on a combination of clinical rationale and feasibility. Whilst, one could have investigated  
13 any number of combinations of the six conditions, the better and preferred approach taken  
14 was to group conditions first at the "vascular" level. As highlighted earlier, diabetes,  
15 ischaemic heart disease and cerebrovascular disease have shared pathogenesis and  
16 there may be over-lapping of drug treatments. However, the "non-vascular" group  
17 constitute individual chronic conditions with distinct and un-related drug treatments. This  
18 approach enabled comorbidity definitions based on (i) group-level i.e. vascular  
19 comorbidity with one of the non-vascular conditions and (ii) counts i.e. number of other  
20 conditions for each of the six index groups. The study focus was also on comorbidity and  
21 further research is also required on how multimorbidity, defined as two or more conditions,  
22 influences the overall prescribing of multiple drugs and when the unit of analysis for  
23 outcome is not the disease but the arguably more important patient-centred outcomes.  
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32 The large scale study of specified chronic diseases was conducted using an anonymised  
33 database for a 2-year time-period. In terms of the cross-sectional associations, the  
34 findings on the levels of chronic conditions, comorbidity and multi-drug prescribing do offer  
35 clinical implications as outlined earlier. However, the implications of the associations  
36 between comorbidity and the key drug definitions may be limited in this cross-sectional  
37 design and these may be treated cautiously as emergent findings. The chronic disease  
38 definitions were also based on routinely collected registers from general practices, which  
39 were and are part of a research network dedicated to the collection of clinical data in  
40 actual consultation. Whilst these chronic disease registers may be subject to variations in  
41 recording<sup>32</sup>, the study analyses provide the estimates of association in actual clinical  
42 practice across 11 different sites.  
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49 The drug definitions were based on routinely coded repeat prescriptions and over a 2-year  
50 time-period represent an appropriate measure at the simpler but distinct broad system  
51 category. Patients however will also have been prescribed other drug categories outside  
52 of the five main categories that we had selected and for other less common conditions  
53 from the ones selected in the study, which means these drug levels are a specific  
54 estimate. The construction of our study defined index or 'alone' groups (without the other  
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3 5 conditions) provided the relative multi-drug level estimates to when the index condition  
4 was comorbid with one of the other 5 conditions. So the multi-drug levels in the 'alone'  
5 group provide an estimate of main drug system prescribing without the associated  
6 condition (i.e. for other indications) compared to levels when there is a clear comorbidity  
7 record. However, this is time-defined by a 2-year time window, so some mis-classification  
8 may be possible and further research could explore how broad system drug definitions  
9 capture the underlying and specific common diagnostic categories. Further research is  
10 also required for the arguably more complex assimilation of the range of defined drug  
11 categories, other multi-morbidity and to investigate specific effect of individual drugs  
12 categories. Most of these drugs, other than analgesia such as anti-inflammatories, are not  
13 available over the counter and are usually clinician prescribed. So it is possible that  
14 common over the counter drugs, particularly in relation to osteoarthritis, may be an under-  
15 estimate; however, the selection of repeated prescribing would mitigate against such  
16 under-estimation. Finally, although a large scale study, these general practices are drawn  
17 from one region of England, and whilst this might limit generalisability, the internal validity  
18 of the findings still remains.

19  
20 In conclusion, our study findings show the links between common chronic conditions,  
21 comorbidity and associated multi-drug prescribing. The key and distinct finding is that the  
22 study shows that multi-drug prescribing defined by a range of selected but different  
23 systems is high in chronic conditions and higher in comorbidity. The common group of  
24 vascular conditions are not the only ones associated with their 'own' guideline driven  
25 multi-drug therapy, but the addition of non-vascular conditions such as COPD, OA and  
26 depression adds to the multi-drugs burden in patients. The importance of these findings,  
27 in addition to quantifying the scale, is whether such multi-drug therapy influences the  
28 quality of care for each of the individual conditions. Our findings suggest the potential for  
29 sub-optimal drug treatment as a consequence is in line with other evidence<sup>33</sup>, but further  
30 research is required to investigate the impact of disease status, comorbidity, multi-drug  
31 therapy on prospective and long-term outcomes of clinical care.  
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**Data sharing:** Data is not available for sharing under existing governance arrangements and no additional data is available.

**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 <sup>†</sup>
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	Beta 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	n/a	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 anti-diabetic 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

<sup>†</sup>Population refers to those with one of six chronic conditions ( $n = 12875$ ), which included hypertension, diabetes, coronary heart disease, cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD), osteoarthritis (OA) and depression; Drug categories are based on the British National Formulary (BNF) classification

Table 2: Socio-demographic characteristics of the main drug categories

Factor	Total Numbers	Main drug categories				Musculo-skeletal System
		Cardiovascular system	Respiratory System	Central-nervous System	Endocrine System	
<b>Age (years)</b>						
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 years and over	715	608 (85)	135 (19)	513 (72)	101 (14)	59 (8)
<b>Gender</b>						
Women	6896	4813 (70)	1510 (22)	4528 (66)	1351 (20)	1260 (18)
Men	5979	4571 (76)	1351 (23)	2950 (49)	1565 (26)	883 (15)
<b>Deprivation**</b>						
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 sub-group

Table 3: Associations between individual study groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (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 (3.0-4.2)
<i>Prevalence ratio</i>	<i>0.2</i>	<i>0.4</i>	<i>0.5</i>	<i>1.5</i>	<i>2.3</i>	<i>3.3</i>	
CHD 'alone'	148	4057	4248	1372	160	16	1.0
CHD comorbidity	36	1027	3973	3516	1327	121	5.35 (4.6-6.3)
<i>Prevalence ratio</i>	<i>0.2</i>	<i>0.3</i>	<i>0.9</i>	<i>2.6</i>	<i>8.3</i>	<i>7.6</i>	
CVD 'alone'	688	4087	3848	1306	70	0	1.0
CVD comorbidity	41	1745	4251	3224	678	62	3.70 (2.8-5.0)
<i>Prevalence ratio</i>	<i>0.1</i>	<i>0.4</i>	<i>1.1</i>	<i>2.5</i>	<i>9.7</i>	<i>n/a</i>	
COPD 'alone'	940	2487	3496	2726	350	0	1.0
COPD comorbidity	189	946	2855	4117	1751	142	3.22 (2.6-4.0)
<i>Prevalence ratio</i>	<i>0.20</i>	<i>0.4</i>	<i>0.8</i>	<i>1.5</i>	<i>5.00</i>	<i>n/a</i>	
OA 'alone'	1378	2786	3722	1854	256	5	1.0
OA comorbidity	174	1260	3550	3420	1325	271	3.64 (3.1-4.3)
<i>Prevalence ratio</i>	<i>0.1</i>	<i>0.5</i>	<i>1.0</i>	<i>1.8</i>	<i>5.2</i>	<i>54</i>	
Depression 'alone'	1912	4140	3093	776	79	0	1.0
Depression comorbidity	325	1422	3555	3555	1082	62	7.11 (5.6-9.0)
<i>Prevalence ratio</i>	<i>0.17</i>	<i>0.34</i>	<i>1.15</i>	<i>4.58</i>	<i>13.7</i>	<i>n/a</i>	

\*Alone – people with disease alone and none of the other 5 morbidities, comorbidity is 1 or more of other 5 study morbidities, \*\*Comorbid drug 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 to 4 combined) compared to lower drug counts (2 or less), CHD is coronary heart disease and CVD is cerebro-vascular disease

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**Table 4: Associations between vascular comorbidity groups and higher multi-drug counts**

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (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 (3.8-5.7)
<i>Prevalence ratio</i>	<i>0.43</i>	<i>0.29</i>	<i>0.71</i>	<i>1.65</i>	<i>2.60</i>	<i>1.90</i>	
Vascular group and OA	29	873	3493	3697	1557	349	3.01 (2.6-3.5)
<i>Prevalence ratio</i>	<i>0.15</i>	<i>0.37</i>	<i>0.87</i>	<i>1.45</i>	<i>2.01</i>	<i>3.92</i>	
Vascular group and Depression	69	829	3733	3917	1359	92	3.22 (2.6-3.9)
<i>Prevalence ratio</i>	<i>0.35</i>	<i>0.35</i>	<i>0.93</i>	<i>1.54</i>	<i>1.76</i>	<i>1.03</i>	

\*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 to 4 combined) compared to lower drug counts (2 or less)

**Table 5: Key drug treatment of non-vascular conditions in vascular comorbidity**

Numbers (%)	Key drug treatments		Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (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 (0.43-0.78)	0.55 (0.40-0.75)
OA without vascular comorbidity	281 (16)	1440 (84)	1.0	1.0
OA and vascular comorbidity	117 (17)	568 (83)	0.95 (0.75-1.20)	0.82 (0.64-1.06)
Depression without vascular comorbidity	259 (16)	1378 (84)	1.0	1.0
Depression and vascular group	120 (28)	311 (72)	0.49 (0.38-0.62)	0.55 (0.42-0.73)

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

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1 | **Title: Chronic condition comorbidity and multi-drug therapy in general practice**

2 | **populations: a cross-sectional linkage study**

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25 | *Key words: co-morbidity; drug therapy; chronic disease; depression; epidemiology*

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1 *Abstract*

2 **Objectives:** The study investigated (i) the association between comorbidity and multi-drug  
3 prescribing compared to the index condition, and (ii) the association between vascular  
4 comorbidity and non-vascular condition optimal prescribing.

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

7 **Setting:** 11 general practices in North Staffordshire, England.

8 **Participants:** ~~Study groups~~ Study population was aged 40 years and over (N=12,875)  
9 were: (i) six chronic condition groups, (ii) combined vascular group (at least one of  
10 diabetes mellitus, cardiovascular disease or cerebrovascular disease) and (iii) non-  
11 vascular conditions with chronic obstructive pulmonary disease, osteoarthritis or  
12 depression). Within six conditions, comorbidity with the other 5 conditions was compared  
13 to index 'alone' group without them. Additionally how the 'vascular' (one of diabetes,  
14 cardiovascular disease and cerebrovascular disease) comorbidity influenced COPD, OA  
15 or depression drug prescribing was investigated.

16 **Outcome Measures:** Based on the British National Formulary, five main drug chapters  
17 constituted a measure of drug counts, with low count as 2 or less and high multi-drug  
18 count as 3 or more. ~~Optimal group of~~ Key drugs prescribed for COPD, OA and depression  
19 were derived from guidelines.

20 **Results:** The adjusted associations between the comorbid groups and higher multi-drug  
21 count compared to their respective 'alone' group were: Odds ratio 7.1 (95% Confidence  
22 Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7  
23 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0  
24 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

25 In COPD, vascular comorbidity was associated with a significant reduction in optimal-key  
26 COPD drug treatments (adjusted Odds Ratio 0.6 (95% confidence interval 0.4 to 0.8). In  
27 depression, vascular comorbidity was associated with a reduction in optimal-key  
28 depression drug treatments (OR 0.6 (0.4 to 0.7)).

29 **Conclusions:** ~~The study shows~~ Our findings that show multi-drug prescribing defined by a  
30 range of selected but for different body systems, is higher with comorbidity and may be  
31 associated with sub-optimal lower likelihood of prescribing for specific conditions. The  
32 importance of these findings is Further research is required on whether such as multi-drug  
33 therapy prescribing influences the outcomes of care for chronic conditions.

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1 **Article summary**

2 ***Strengths and limitations of this study***

- 3 • The study was based on large-scale data linking common chronic conditions from  
4 general practice populations to prescription data over a 2-year time-period.
- 5 • The study highlights the innovative approach to multi-drug measurement which  
6 accounts for vascular condition-specific drugs as well as summarising non-  
7 vascular co-drug therapy.
- 8 • The study provides the emergent approach to investigating the influence of multi-  
9 drug therapy on potentially 'optimal' drug prescribing in populations.
- 10 • The study uses a specific but limited number of common chronic conditions to  
11 illustrate the approach to linking comorbidity and multi-drug data within a single  
12 large region of the UK.
- 13 • The study used overall broad measures of drug prescribing and further research is  
14 required to understand the specific influence of multi-drug dose and duration on  
15 longer-term outcomes.

## 1 Introduction

2 ~~Many older people experience two or more morbidities at the same time, defined as~~  
 3 ~~multimorbidity, and within this~~ Comorbidity is defined as other co-occurring diseases in  
 4 the same individual with an index condition,<sup>1,2</sup> ~~and is~~ These are important concepts as  
 5 ~~other-the experience of multiple~~ conditions ~~at the same time~~ may influence the  
 6 progression and treatment of ~~the-an~~ index condition.<sup>4</sup> Current evidence of the overall  
 7 implications of chronic diseases, have shown that this phenomenon is associated with  
 8 adverse health, increased health care utilisation and increased mortality.<sup>23,34,4,5</sup> Although  
 9 the health impact of chronic disease comorbidity has been studied, there have been few  
 10 studies on how chronic diseases comorbidity might influence drug use and related clinical  
 11 decisions especially in general practice. This is a significant evidence gap despite the fact  
 12 that drug~~s~~ interventions feature routinely in many disease guidelines. Currently, the model  
 13 for managing chronic diseases focuses on treating individual conditions, and patients may  
 14 on the one hand benefit from the drug treatment of each of their chronic conditions;  
 15 however there is a risk of multiple drug therapy, side effects and drug interactions which  
 16 could in combination be detrimental.<sup>66,67</sup>

17 Many national health care policies have developed frameworks for chronic disease  
 18 models of care and specific guidelines for the optimal management of chronic diseases.  
 19 Examples include policy and guidelines for the common conditions in the general  
 20 population with diabetes, ischaemic heart disease, stroke, chronic obstructive airways  
 21 disease and depression.<sup>7,8,9,10,11,12</sup> In addition, these guidelines are beginning to be  
 22 adapted for the common experience of comorbid conditions, particularly by older people,  
 23 for each of these individual conditions.<sup>12-13</sup> Since people with one or more chronic  
 24 conditions are increasing in number, this has increasingly brought in focus the scale and  
 25 quantity of multiple drug prescribing in general populations. The key questions then  
 26 become (i) how does multiple drug prescribing relate to the primary index condition and (ii)  
 27 how does multiple drug prescribing escalate when populations experience multiple  
 28 conditions which might be directly linked or occur by chance together. The cardio-  
 29 metabolic diseases, such as hypertension, diabetes, heart disease and cerebrovascular  
 30 disease share aetiology and common drug treatment pathways, but it is still important to  
 31 understand the scale of multiple drug therapy that might be associated when these  
 32 conditions co-occur together in the same individual. Many chronic diseases also have  
 33 conditions which are related to mechanisms other than patho-physiology. For example,  
 34 other common chronic conditions include chronic obstructive airways disease and

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1 depression, and this epidemiology provides the scale of multiple drug therapies when co-  
2 occurring conditions might be un-related.

3 In terms of the current evidence in this field, much of it has focused around  
4 'polypharmacy' studies.<sup>43,14,44,15,45,16</sup> However, whilst this might seem an appropriate broad  
5 umbrella term, in research and clinical approaches, it has often focused on ~~multiple~~  
6 ~~arbitrarily chosen number of~~ drugs, and ~~linked the term to either inappropriate prescribing~~  
7 ~~or associated~~ adverse ~~associated~~ events in older populations.<sup>16</sup> ~~This lack of consensus~~  
8 ~~defined approach to this problem has led to an argument for less ambiguous~~  
9 ~~terminology~~,<sup>17</sup> and we propose that 'multi-drug' therapy is used to link in with the standard  
10 ~~approach to two or more conditions, which is 'multi-morbidity'~~. Within this evidence, ~~this~~  
11 ~~there is still creates thea clear gap of in~~ how ~~multimorbidityple conditions~~ link to  
12 ~~multidrugple drugs~~ prescribing, and whether comorbidity influences the ~~drug optimal~~  
13 prescribing ~~of for~~ an index disease.

14 In this study, the focus was on six common chronic conditions in the general population,  
15 which included diabetes mellitus, cardiovascular diseases, cerebrovascular diseases  
16 chronic obstructive pulmonary diseases, osteoarthritis and depression. The choice of  
17 these chronic conditions for the purpose of the study is based on a number of factors  
18 including the epidemiology, especially prevalence of the diseases, as well as aetio-  
19 pathogenesis and impacts on quality of life and psychological well-being. For example,  
20 while diabetes mellitus, coronary heart disease and cerebrovascular diseases have a  
21 common pathological basis of causation (the 'vascular group'), and often co-exist in one  
22 patient, they are also known to have high mortality rates - hence the drive towards  
23 measures aimed at optimising the management of these diseases.<sup>46,18,47,19</sup> The other  
24 three, non-vascular chronic conditions - ~~Chronic-chronic~~ Obstructive ~~P~~pulmonary  
25 ~~D~~disease (COPD), ~~Osteoarthritis-osteoarthritis~~ (OA) and ~~Depression-depression~~ are  
26 leading causes of morbidity, high cost of care and psychological distress respectively.  
27 <sup>18,19,20,21,22</sup> ~~The rationale for our focus on few selected common conditions was also to~~  
28 ~~provide common comorbidity combinations which are potentially treated with drugs as a~~  
29 ~~key intervention.~~

30 ~~In this study, we investigated two separate issues using the selected group of vascular~~  
31 ~~and non-vascular conditions. First, we in addition to wanted to~~ investigate the relative  
32 multi-~~ple~~ drugs prescribing in ~~comorbidity compared to one of the~~ for each of six ~~chosen~~  
33 index examples, ~~comparing comorbid groups with prescribing levels in the respective~~

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1 ~~index groups. Second, there was also a~~ wanted to test of whether vascular comorbidity  
2 influenced ~~optimal key~~ drug prescribing for chosen conditions. The vascular group were  
3 likely to be on similar multiple drugs, so the distinct hypothesis was tested, that was drug  
4 prescribing in vascular conditions overall may influence key drug prescribing in the  
5 individual non-vascular conditions of COPD, OA or depression.

6 ~~The patients were classified into the individual condition groups, and then two specific~~  
7 ~~study groups were constructed: vascular group (population with at least one of diabetes~~  
8 ~~mellitus, cardiovascular disease or cerebrovascular disease) and non-vascular group of~~  
9 ~~individual conditions (chronic obstructive pulmonary disease, osteoarthritis or depression).~~  
10 ~~The individual groups enabled the comparison of index groups to those with comorbidity.~~  
11 ~~The vascular group were likely to be on similar multiple drugs, so a separate hypothesis~~  
12 ~~was tested, that was prescribing in vascular conditions overall may influence prescribing~~  
13 ~~in the individual non-vascular conditions of chronic obstructive pulmonary disease,~~  
14 ~~osteoarthritis and depression.~~

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## 17 Methods

18 **Design and Study population:** The cross-sectional study was conducted using two  
19 linked databases on patients aged 40 years and over presenting to general practice over  
20 a 2-year time period (from 1<sup>st</sup> January 2002 to 31<sup>st</sup> December 2003). ~~We wanted to~~  
21 ~~investigate what multi-drug prescribing levels were before a national UK performance-~~  
22 ~~based incentive (Quality outcomes Framework) was implemented to test the associations~~  
23 ~~between comorbidity and routine multi-drug prescribing. Ethical approval for the use of~~  
24 ~~these anonymised databases was granted by the North Staffordshire Research Ethics~~  
25 ~~Committee~~

26 **Settings:** The clinical and prescription databases analysed were derived from an  
27 anonymised computer recorded consultations from eleven general practices from the  
28 North Staffordshire Keele GP research partnership. The partnership covers a range of  
29 practices covering varying socioeconomic groups within rural and urban areas and has  
30 been involved in data collection over time for the purpose of epidemiological studies.  
31 There is an on-going process of data validation to improve data quality, and there is  
32 evidence that this measure improves data recording by general practitioners and their  
33 teams.<sup>24,23</sup>

1 **Chronic disease data:** The Consultation in Primary Care Archive (CIPCA) database  
2 focuses on the routinely collected morbidity encounters in actual consultations and coded  
3 using a standard clinical classification (Read codes).<sup>22-24</sup> Patients who had a record of a  
4 disease-specific READ coded morbidity of interest were included in the study and the  
5 main codes were used with all associated “daughter codes”. The main READ codes that  
6 were used to define the chronic disease groups were: diabetes mellitus (Read codes  
7 C10), cardiovascular diseases (ischaemic heart disease (G3); heart failure (G58),  
8 excluding hypertension)), cerebrovascular diseases (G6), chronic obstructive pulmonary  
9 disease (H30, excluding asthma) (COPD), osteoarthritis (N05, excluding arthralgia), and  
10 depression (E11, E20, Eu and excluding psychosis).

### 11 **Study groups: definitions**

12 ~~The patients were classified into the individual condition groups, and then two specific~~  
13 ~~study groups were constructed: vascular group (population with at least one of diabetes~~  
14 ~~mellitus, cardiovascular disease or cerebrovascular disease) and non-vascular group of~~  
15 ~~individual conditions (chronic obstructive pulmonary disease, osteoarthritis or depression).~~  
16 ~~The individual groups enabled the comparison of index groups to those with comorbidity.~~  
17 ~~The vascular group were likely to be on similar multiple drugs, so a separate hypothesis~~  
18 ~~was tested, that was prescribing in vascular conditions overall may influence prescribing~~  
19 ~~in the individual non-vascular conditions of chronic obstructive pulmonary disease,~~  
20 ~~osteoarthritis and depression.~~

### 21 **Comorbidity: definitions**

22  
23 There were two approaches to defining comorbidity. First, comorbidity was defined as the  
24 presence of one of the other five selected conditions. So using the diabetes population as  
25 an example, the diabetes ‘index’ group was defined as diabetes ‘alone’ and without  
26 anyone of the other five conditions, whereas diabetes ‘comorbid’ group was defined as at  
27 least one of the other five conditions. The index ‘alone’ group would also enable the  
28 capture of the other morbidity that was outside of the study selected conditions. This  
29 definition was applied to each of the six chronic conditions individually. Second, in the  
30 vascular group, comorbidity was defined separately as the individual and specific addition  
31 of COPD, OA or depression, and irrespective of whether the latter three occurred  
32 together.  
33

34 ~~The approach taken to looking at specific groups and conditions was based on a~~  
35 ~~combination of clinical rationale and feasibility. Whilst, 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 over lapping of drug treatments. However, the “non vascular” group constitute individual chronic conditions with distinct and un-related drug treatments. This approach enabled comorbidity definitions based on (i) group level i.e. vascular comorbidity with one of the non-vascular conditions and (ii) counts i.e. number of other conditions for each of the six index groups.~~

#### **PPrescribed drug measure: overall multi-drug 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.<sup>23,25</sup> The BNF consists of 15 main chapters based on the systems of the body, and within which there are further sub-sections 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 multi-drug counts. The BNF chapter for cardiovascular and cerebrovascular drugs were under BNF chapter 2, for COPD drugs under chapter 3, for depression under chapter 4, for diabetes mellitus under chapter 6, and for osteoarthritis 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 multi-drug count definition in this approach would then specifically relate to people prescribed drugs from at least two or more of the five chapters indicated.

#### **Prescribed drug measure Vascular comorbidity and drug :- optimal drug definitions prescribing for non-vascular conditions**

~~Optimal-~~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

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1 of diabetes, cardiovascular disease and cerebrovascular disease. The non-vascular  
2 groups were then individually compared with and without vascular comorbidity. For  
3 example, the COPD group was compared with vascular comorbidity to the COPD without  
4 vascular comorbidity, in relation to the likelihood of receiving COPD-specific drug  
5 treatment.

6 Whilst ~~optimal~~ the key drug treatments ~~of for these conditions~~ COPD, OA and depression  
7 can be examined in different ways such as the use of specific drugs, or drug doses and  
8 duration of drug therapy, we wanted to first establish the simplest likelihood of a patient  
9 given ~~any one of an optimal~~ the key group of drugs for COPD, OA or depression. The  
10 ~~optimal~~ group of drugs derived from guidelines for COPD<sup>10</sup> included bronchodilators,  
11 corticosteroids, inhaled steroids, ~~and oxygen~~ mucolytics (BNF sections 3.1, 3.2, 3.5 and  
12 3.6). The ~~optimal~~ group of drugs for ~~osteoarthritis~~<sup>24</sup> -~~osteoarthritis~~<sup>26</sup> included non-opioid  
13 analgesics, opioid analgesics, non-steroidal anti-inflammatories, and Cox 2 inhibitors  
14 (BNF sections 4.7.1, 4.7.2, 10.1.1 and 10.1.2.2). The ~~optimal~~ group of drugs for  
15 depression<sup>11</sup> included hypnotics, anxiolytics and antidepressants (BNF sections 4.1 and  
16 4.3).

## 17 Analysis

18 The first analyses was to describe the 2-year period prevalence of the 5 main BNF  
19 chapters in the specified chronic disease population, with a focus on some of the common  
20 drugs that were prescribed within each chapter expressed as drug prevalence/10,000  
21 population aged 40 years and over, ~~and differences were assessed using Chi-square~~  
22 ~~tests~~. The five main chapter drug categories prevalence are described by age, gender and  
23 deprivation status. Deprivation was measured by the Index of Multiple Deprivation (IMD)  
24 which is a composite score that is linked to postal address codes.<sup>25-27</sup> The IMD score was  
25 categorised into the bottom 20% (most deprived), middle 60% and the top 20% score  
26 (most affluent).

27 For each of the six chronic conditions, associations between the comorbid groups and  
28 higher multi-drug counts were compared to the respective reference 'alone' group. The  
29 'outcome' of higher multi-drug therapy was defined as 3 or more of the chapter counts and  
30 compared to 2 counts or less. Associations ~~using logistic regression~~ were expressed as  
31 Odds Ratios (OR) with 95% confidence intervals (CI), and also included the ratios  
32 comparing prevalence of each drug count category in the comorbid group compared to  
33 the 'alone' group. Then for the vascular group, associations between each of the comorbid

1 group with COPD, OA or depression were compared to the vascular 'alone' alone and higher multi-drug counts were then estimated.

3 Finally, the data was analysed for the study defined optimal drug treatments for COPD, OA or depression. Three study groups constructed were: COPD and 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 the compared to their respective vascular group e.g. COPD and vascular group compared to COPD without a vascular condition, by the specific optimal drug treatment. Association estimates are presented both as unadjusted and adjusted figures with 95% confidence intervals. Analyses were carried out using SPSS version 17.0 statistical software.

## 11 Results

### 12 Study population

13 In the study population of 12,875 aged 40 years and over, the 2-year time-period prevalence estimated per 10,000 for number of patients prescribed with the cardiovascular system drugs was 9,384 (2-year time-period prevalence 73%), for respiratory system drugs were 2,861 (22%), for non-opioid analgesia were 5,395 (42%), for anti-depressants were 2,517 (25%), for anti-diabetic drugs were 2,916 (22.6%) and musculoskeletal system anti-inflammatory drugs was 2,143 (17%) (Table 1).

20 In terms of the socio-demographic distribution, older patients aged 70 years and over and populations in the top 20% deprivation status were significantly more likely to be prescribed all five main drug categories, except for the cardiovascular system (Chi-square test for trend  $p < 0.001$ ). For women compared to men, there was variation by type of main drug category; the comparative 2-year prevalence figures by gender were significantly higher for men compared to 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 to women for anxiolytics and anti-depressants (49% vs 66%) and anti-inflammatories (15% vs 18%) (Chi square test  $p < 0.001$  (Table 2)).

### 29 Individual chronic condition comorbidity and higher multi-drug counts

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1 For all six specified chronic conditions, at lower drugs counts of up to 2, the prevalence  
2 numbers were greater for the individual groups without the other five comorbid conditions  
3 compared to the numbers for the individual conditions with comorbidity of other five  
4 conditions (**Table 3**). For the drug count of 2 different chapters, the comorbid to 'alone'  
5 ratios ranged from 1.15 for the depression group to 0.5 for the diabetes group. The  
6 prevalence ratios were highest for the multi-drug count of 4, and these ranged from 13.7  
7 for the depression comorbid group to 2.3 for diabetes comorbid group.

8 Adjusting for age, gender and deprivation, the associations between the comorbid groups  
9 and higher multi-group count compared to their respective 'alone' group ordered by  
10 strength of association were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for  
11 depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for  
12 cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for  
13 diabetes, and OR 3.2 (2.6 to 4.0) for COPD.

#### 14 **Vascular condition comorbidity and higher multi-drug counts**

15 The prevalence ratios for the multi-drug count of 5 ranged from 3.9 for vascular group  
16 comorbid with osteoarthritis, to 1.9 for vascular group comorbid with COPD, and 1.0 for  
17 the vascular group comorbid with depression (**Table 4**). Adjusting for age, gender and  
18 deprivation, the associations between the comorbid groups and higher multi-group count  
19 compared to their respective 'alone' group ordered by strength of association were: Odds  
20 ratio 4.6 (95% Confidence Intervals 3.8 to 5.7) for vascular group comorbid with COPD,  
21 OR 3.2 (2.6 to 3.9) for vascular group comorbid with depression, and vascular group  
22 comorbid with OA OR 3.0 (2.6 to 3.5).

#### 23 **Comorbid vascular conditions and optimal non-vascular condition prescribing**

24 The three specific non-vascular groups of COPD, OA and depression were compared with  
25 comorbid vascular conditions to without such vascular comorbidity in terms of their  
26 respective optimal drug treatment (**Table 5**). Adjusting for age, gender and deprivation,  
27 the association between the COPD and vascular comorbid groups compared to their  
28 respective group without vascular conditions showed a significant reduction in optimal  
29 COPD drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.8).  
30 Adjusting for age, gender and deprivation, the association between the depression and  
31 vascular comorbid groups compared to their respective group without vascular conditions  
32 showed a significant reduction in optimal depression drug treatment with an Odds Ratio of

1 0.6 (95% confidence interval 0.4 to 0.7). Adjusting for age, gender and deprivation, the  
2 association between the OA and vascular comorbid groups compared to their respective  
3 group without vascular conditions did not show a statistically significant reduction in  
4 optimal OA drug treatment with an Odds Ratio of 0.8 (95% confidence interval 0.6 to 1.1).

## 5 Discussion

6 Our findings from a large cross-sectional study of nearly 13,000 patients aged 40 years  
7 and over with one of six specified and common chronic conditions showed the scale of  
8 multi-drug prescribing, which was higher in the presence of comorbidity compared to the  
9 respective index groups. Whilst previous evidence has shown the high levels of [multiple  
10 drug prescribing/polypharmacy](#)<sup>15</sup>, our study findings link the disease status, comorbidity  
11 status to the measure of multi-drug prescribing.

12 Depending on whether the chronic conditions were vascular (diabetes, cardiovascular or  
13 cerebrovascular) or the non-vascular (COPD, OA or depression), the higher levels of  
14 multi-drug prescribing varied. All six conditions with comorbidity compared to their index  
15 condition had much higher multi-drug count, even adjusting for age, gender and  
16 deprivation. The measure of multi-drug count was notably distinct by the use of five  
17 different main drug chapter categories which were for different body systems, which  
18 means that this 'outcome' was not about multiple drugs use for the same condition. For  
19 example, a diabetic with a higher multi-drug count of 4 or 5 in this study relates to different  
20 and distinct body systems, and not to the different drugs under the same chapter. The  
21 chronic condition of depression comorbidity had the strongest strength of association with  
22 higher multi-drug counts, followed by cardiovascular disease comorbidity, and the  
23 estimates of association for cerebrovascular disease, osteoarthritis and diabetes were  
24 similar. These findings suggest that the index condition and comorbidity may influence the  
25 range of multi-drug prescribing, and generates the interesting hypothesis on the potential  
26 variation in clinical outcomes of the index conditions may be because of underlying  
27 comorbid drug prescribing.

28  
29 The study also grouped the vascular-related conditions to investigate the influence of non-  
30 vascular drug prescribing compared to vascular conditions 'alone' (i.e. without any one of  
31 COPD, OA or depression). Again, the adjusted associations were significant, with  
32 vascular comorbidity being associated with higher-multi-drug counts compared to the  
33 respective 'vascular index' group. Here the clinical implication is that vascular comorbidity  
34 in populations aged 40 years and over might not only be associated with multiple vascular  
35 drugs as routinely suggested by clinical [guidelines](#)<sup>26</sup> [guidelines](#)<sup>28</sup>, but by a range of

1 conditions such as comorbidity of COPD, OA or depression. It is possible that these  
 2 conditions and the drug treatments for them may also in the end influence the health and  
 3 healthcare outcomes of the index vascular conditions.<sup>27,29</sup>

4 In terms of the influence of comorbidity on ~~optimal~~key drug prescribing, our study findings  
 5 show that vascular comorbidity in COPD and depression is associated with ~~sub-~~  
 6 ~~optimal~~lower likelihood of drug prescribing for the respective conditions of COPD and  
 7 depression. Similar findings, particularly for sub-optimal depression drug treatment, when  
 8 depression is comorbid with chronic disease has been shown previously.<sup>28,30,29-31</sup> However,  
 9 such findings for osteoarthritis were not found, and here it is possible that the 'outcome' of  
 10 analgesia was too broad, as analgesia use covers a range of other painful conditions, in  
 11 addition to osteoarthritis. Although the ~~optimal~~key drug definition was simple and broad,  
 12 our study findings seem to suggest that comorbidity does influence ~~optimal~~drug  
 13 prescribing ~~for specific conditions, and further reasons for this might dis-entangle whether~~  
 14 ~~it is due to drug therapeutic or diagnostic conflicts. Whether this is due to some kind of~~  
 15 ~~therapeutic inertia or is due to GPs' reasoned consideration of drug-drug and drug-~~  
 16 ~~disease interactions and the overall well-being of the patient is the important question~~  
 17 ~~raised by the findings.~~

19 ~~The approach taken to looking at specific groups and six common conditions was based~~  
 20 ~~on a combination of clinical rationale and feasibility. Whilst, one could have investigated~~  
 21 ~~any number of combinations of the six conditions, the better and preferred approach taken~~  
 22 ~~was to group conditions first at the "vascular" level. As highlighted earlier, diabetes,~~  
 23 ~~ischaemic heart disease and cerebrovascular disease have shared pathogenesis and~~  
 24 ~~there may be over-lapping of drug treatments. However, the "non-vascular" group~~  
 25 ~~constitute individual chronic conditions with distinct and un-related drug treatments. This~~  
 26 ~~approach enabled comorbidity definitions based on (i) group-level i.e. vascular~~  
 27 ~~comorbidity with one of the non-vascular conditions and (ii) counts i.e. number of other~~  
 28 ~~conditions for each of the six index groups. The study focus was also on comorbidity and~~  
 29 ~~further research is also required on how multimorbidity, defined as two or more conditions,~~  
 30 ~~influences the overall prescribing of multiple drugs and when the unit of analysis for~~  
 31 ~~outcome is not the disease but the arguably more important patient-centred outcomes.~~

33 The large scale study of specified chronic diseases was conducted using an anonymised  
 34 database for a 2-year time-period. In terms of the cross-sectional associations, the  
 35 findings on the levels of chronic conditions, comorbidity and multi-drug prescribing do offer

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1 clinical implications as outlined earlier. However, the implications of the associations  
2 between comorbidity and optimal drug definitions may be limited in this cross-sectional  
3 design and these may be treated cautiously as emergent findings. The chronic disease  
4 definitions were also based on routinely collected registers from general practices, which  
5 were and are part of a research network dedicated to the collection of clinical data in  
6 actual consultation. Whilst these chronic disease registers may be subject to variations in  
7 ~~recording~~<sup>30</sup>~~recording~~<sup>32</sup>, the study analyses provide the estimates of association in actual  
8 clinical practice across 11 different sites.

9 The drug definitions were based on routinely coded repeat prescriptions and over a 2-year  
10 time-period represent an appropriate measure at the simpler but distinct broad system  
11 category. Patients however will also have been prescribed other drug categories outside  
12 of the five main categories that we had selected and for other less common conditions  
13 from the ones selected in the study, which means these drug levels are a specific  
14 estimate. The construction of our study defined index or 'alone' groups (without the other  
15 5 conditions) provided the relative multi-drug level estimates to when the index condition  
16 was comorbid with one of the other 5 conditions. So the multi-drug levels in the 'alone'  
17 group provide an estimate of main drug system prescribing without the associated  
18 condition (i.e. for other indications) compared to levels when there is a clear comorbidity  
19 record. However, this is time-defined by a 2-year time window, so some mis-classification  
20 may be possible and further research could explore how broad system drug definitions  
21 capture the underlying and specific common diagnostic categories. Further research is  
22 also required for the arguably more complex assimilation of the range of defined drug  
23 categories, other multi-morbidity and to investigate specific effect of individual drugs  
24 categories. Most of these drugs, other than analgesia such as anti-inflammatories, are not  
25 available over the counter and are usually clinician prescribed. So it is possible that  
26 common over the counter drugs, particularly in relation to osteoarthritis, may be an under-  
27 estimate; however, the selection of repeated prescribing would mitigate against such  
28 under-estimation. Finally, although a large scale study, these general practices are drawn  
29 from one region of England, and whilst this might limit generalisability, the internal validity  
30 of the findings still remains.

31 In conclusion, our study findings show the links between common chronic conditions,  
32 comorbidity and associated multi-drug prescribing. The key and distinct finding is that the  
33 study shows that multi-drug prescribing defined by a range of selected but different  
34 systems is high in chronic conditions and higher in comorbidity. The common group of  
35 vascular conditions are not the only ones associated with their 'own' guideline driven  
36 multi-drug therapy, but the addition of non-vascular conditions such as COPD, OA and

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1 depression adds to the multi-drugs burden in patients. The importance of these findings,  
2 in addition to quantifying the scale, is whether such multi-drug therapy influences the  
3 quality of care for each of the individual conditions. Our findings suggest the potential for  
4 sub-optimal drug treatment as a consequence is in line with other **evidence<sup>34</sup>** **evidence<sup>33</sup>**,  
5 but further research is required to investigate the impact of disease status, comorbidity,  
6 multi-drug therapy on prospective and long-term outcomes of clinical care.

For peer review only

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**Contributorship statement:** ER and DG coordinated the study data collection and contributed to the writing of the manuscript. ER, DG 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.

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All authors have contributed and approved the final version of this manuscript.

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**Competing interests:** There are no competing requests.

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**Data sharing:** Data is not available for sharing under existing governance arrangements and no additional data is available.

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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 <sup>†</sup>
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	Beta 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
	3.5	Respiratory stimulants	Dexapram	0	0
	3.6	Oxygen	n/a	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 anti-diabetic 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

<sup>†</sup>Population refers to those with one of six chronic conditions ( $n = 12875$ ), which included hypertension, diabetes, coronary heart disease, cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD), osteoarthritis (OA) and depression; Drug categories are based on the British National Formulary (BNF)

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Table 2: Socio-demographic characteristics of the main drug categories

Factor	Total Numbers	Main drug categories				
		Cardiovascular system	Respiratory System	Central-nervous System	Endocrine System	Musculo-skeletal System
<b>Age (years)</b>						
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 years and over	715	608 (85)	135 (19)	513 (72)	101 (14)	59 (8)
<b>Gender</b>						
Women	6896	4813 (70)	1510 (22)	4528 (66)	1351 (20)	1260 (18)
Men	5979	4571 (76)	1351 (23)	2950 (49)	1565 (26)	883 (15)
<b>Deprivation**</b>						
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 sub-group

**Table 3: Associations between individual study groups and higher multi-drug counts**

Conditions	Multi-drug number/10,000 population					Adjusted Odds Ratio (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 (3.0-4.2)
<i>Prevalence ratio</i>	<i>0.2</i>	<i>0.4</i>	<i>0.5</i>	<i>1.5</i>	<i>2.3</i>	<i>3.3</i>	
CHD 'alone'	148	4057	4248	1372	160	16	1.0
CHD comorbidity	36	1027	3973	3516	1327	121	5.35 (4.6-6.3)
<i>Prevalence ratio</i>	<i>0.2</i>	<i>0.3</i>	<i>0.9</i>	<i>2.6</i>	<i>8.3</i>	<i>7.6</i>	
CVD 'alone'	688	4087	3848	1306	70	0	1.0
CVD comorbidity	41	1745	4251	3224	678	62	3.70 (2.8-5.0)
<i>Prevalence ratio</i>	<i>0.1</i>	<i>0.4</i>	<i>1.1</i>	<i>2.5</i>	<i>9.7</i>	<i>n/a</i>	
COPD 'alone'	940	2487	3496	2726	350	0	1.0
COPD comorbidity	189	946	2855	4117	1751	142	3.22 (2.6-4.0)
<i>Prevalence ratio</i>	<i>0.20</i>	<i>0.4</i>	<i>0.8</i>	<i>1.5</i>	<i>5.00</i>	<i>n/a</i>	
OA 'alone'	1378	2786	3722	1854	256	5	1.0
OA comorbidity	174	1260	3550	3420	1325	271	3.64 (3.1-4.3)
<i>Prevalence ratio</i>	<i>0.1</i>	<i>0.5</i>	<i>1.0</i>	<i>1.8</i>	<i>5.2</i>	<i>54</i>	
Depression 'alone'	1912	4140	3093	776	79	0	1.0
Depression comorbidity	325	1422	3555	3555	1082	62	7.11 (5.6-9.0)
<i>Prevalence ratio</i>	<i>0.17</i>	<i>0.34</i>	<i>1.15</i>	<i>4.58</i>	<i>13.7</i>	<i>n/a</i>	

\*Alone – people with disease alone and none of the other 5 morbidities, comorbidity is 1 or more of other 5 study morbidities, \*\*Comorbid drug 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 to 4 combined) compared to lower drug counts (2 or less), CHD is coronary heart disease and CVD is cerebro-vascular disease

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**Table 4: Associations between vascular comorbidity groups and higher multi-drug counts**

Conditions	Multi-drug number/10,000 population					Adjusted Odds Ratio (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 (3.8-5.7)
<i>Prevalence ratio</i>	<i>0.43</i>	<i>0.29</i>	<i>0.71</i>	<i>1.65</i>	<i>2.60</i>	<i>1.90</i>	
Vascular group and OA	29	873	3493	3697	1557	349	3.01 (2.6-3.5)
<i>Prevalence ratio</i>	<i>0.15</i>	<i>0.37</i>	<i>0.87</i>	<i>1.45</i>	<i>2.01</i>	<i>3.92</i>	
Vascular group and Depression	69	829	3733	3917	1359	92	3.22 (2.6-3.9)
<i>Prevalence ratio</i>	<i>0.35</i>	<i>0.35</i>	<i>0.93</i>	<i>1.54</i>	<i>1.76</i>	<i>1.03</i>	

\*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 to 4 combined) compared to lower drug counts (2 or less)



Table 5: **Optimal-Key** drug treatment of non-vascular conditions in vascular comorbidity

Numbers (%)	<b>Optimal-Key</b> drug treatments		Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (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 (0.43-0.78)	0.55 (0.40-0.75)
OA without vascular comorbidity	281 (16)	1440 (84)	1.0	1.0
OA and vascular comorbidity	117 (17)	568 (83)	0.95 (0.75-1.20)	0.82 (0.64-1.06)
Depression without vascular comorbidity	259 (16)	1378 (84)	1.0	1.0
Depression and vascular group	120 (28)	311 (72)	0.49 (0.38-0.62)	0.55 (0.42-0.73)

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

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cross-sectional studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
<b>Methods</b>			
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) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
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	5-7
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	n/a
<b>Results</b>			

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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	8
		(b) Give reasons for non-participation at each stage	n/a
		(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	8
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers of outcome events or summary measures	8-9
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	8-9
		(b) Report category boundaries when continuous variables were categorized	n/a
		(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	n/a
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	9-10
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	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
<b>Other information</b>			
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	11

\*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](http://www.strobe-statement.org).

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2014-005429.R2
Article Type:	Research
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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Cardiovascular medicine, Respiratory medicine, Mental health, Rheumatology, Pharmacology and therapeutics
Keywords:	EPIDEMIOLGY, CARDIOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine), RHEUMATOLOGY, MENTAL HEALTH, THERAPEUTICS

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**Title: Chronic condition comorbidity and multi-drug therapy in general practice  
populations: a cross-sectional linkage study**

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*Key words: co-morbidity; drug therapy; chronic disease; depression; epidemiology*

*Main text count: 3898*

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3 *Abstract*  
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5 **Objectives:** The study investigated (i) the association between comorbidity and multi-drug  
6 prescribing compared to the index condition, and (ii) the association between vascular  
7 comorbidity and non-vascular condition key drug prescribing.  
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10 **Design:** Cross-sectional study linking anonymised computer consultations with  
11 prescription records for a 2-year time-period.  
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13 **Setting:** 11 general practices in North Staffordshire, England.  
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15 **Participants:** Study groups aged 40 years and over (N=12,875). Within six conditions,  
16 comorbid group with the other 5 conditions was compared to an 'alone' group without  
17 them. Additionally how the 'vascular' (one of diabetes, cardiovascular disease and  
18 cerebrovascular disease) comorbidity influenced COPD, OA or depression drug  
19 prescribing was investigated.  
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22 **Outcome Measures:** Based on the British National Formulary, five main drug chapters  
23 constituted a measure of drug counts, with low count as 2 or less and high multi-drug  
24 count as 3 or more. Key drugs prescribed for COPD, OA and depression were derived  
25 from guidelines.  
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28 **Results:** The adjusted associations between the comorbid groups and higher multi-drug  
29 count compared to their respective 'alone' group were: Odds ratio 7.1 (95% Confidence  
30 Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7  
31 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0  
32 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.  
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35 In COPD, vascular comorbidity was associated with a significant reduction in key COPD  
36 drug treatments (adjusted Odds Ratio 0.6 (95% confidence interval 0.4 to 0.8). In  
37 depression, vascular comorbidity was associated with a reduction in key depression drug  
38 treatments (OR 0.6 (0.4 to 0.7)).  
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41 **Conclusions:** Our findings show multi-drug prescribing for different body systems is  
42 higher with comorbidity and may be associated with lower likelihood of prescribing for  
43 specific conditions. Further research is required on whether multi-drug prescribing  
44 influences the outcomes of care for chronic conditions.  
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## Article summary

### *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 multi-drug measurement which accounts for vascular condition-specific drugs as well as summarising non-vascular co-drug therapy.
- The study provides the emergent approach to investigating the influence of multi-drug 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 multi-drug 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 multi-drug 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.<sup>1,2</sup> 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, have shown that this phenomenon is associated with adverse health, increased health care utilisation and increased mortality.<sup>3,4,5</sup> 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.<sup>6,7</sup>

Many national health care 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.<sup>8,9,10,11,12</sup> 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.<sup>13</sup> 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 (i) how does multiple drug prescribing for different systems relate to the primary index condition and (ii) how does multiple drug prescribing escalate when populations experience multiple conditions which might be directly linked or occur by chance together. The cardio-metabolic 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 patho-physiology. For example, other common chronic conditions include chronic obstructive airways disease and

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3 depression, and this epidemiology provides the scale of multiple drug therapies when co-  
4 occurring conditions might be un-related.  
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8 In terms of the current evidence in this field, much of it has focused around  
9 'polypharmacy' studies.<sup>14,15,16</sup> However, whilst this might seem an appropriate broad  
10 umbrella term, in research and clinical approaches, it has often focused on arbitrarily  
11 chosen number of drugs, and linked the term to either inappropriate prescribing or  
12 associated adverse events in older populations.<sup>16</sup> This lack of consensus defined  
13 approach to this problem has led to an argument for less ambiguous terminology<sup>17</sup>, and  
14 we propose that 'multi-drug' therapy is used to link in with the standard approach to two or  
15 more conditions, which is 'multi-morbidity'. Within this evidence, there is still a clear gap in  
16 how morbidity link to drug prescribing, and whether comorbidity influences the drug  
17 prescribing for an index disease.  
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24 In this study, the focus was on six common chronic conditions in the general population,  
25 which included diabetes mellitus, cardiovascular diseases, cerebrovascular diseases  
26 chronic obstructive pulmonary diseases, osteoarthritis and depression. The choice of  
27 these chronic conditions for the purpose of the study was based on a number of factors  
28 including the epidemiology, especially prevalence of the diseases, as well as aetio-  
29 pathogenesis and impacts on quality of life and psychological well-being. For example,  
30 while diabetes mellitus, coronary heart disease and cerebrovascular diseases have a  
31 common pathological basis of causation (the 'vascular group'), and often co-exist in one  
32 patient, they are also known to have high mortality rates - hence the drive towards  
33 measures aimed at optimising the management of these diseases.<sup>18,19</sup> The other three,  
34 non-vascular chronic conditions - chronic obstructive pulmonary disease (COPD),  
35 osteoarthritis (OA) and depression are leading causes of morbidity, high cost of care and  
36 psychological distress respectively.<sup>20,21,22</sup> The rationale for our focus on few selected  
37 common conditions was also to provide common comorbidity combinations which are  
38 potentially treated with drugs as a key intervention.  
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48 We investigated two separate issues using the selected group of vascular and non-  
49 vascular conditions. First, we wanted to investigate the relative multi-drug prescribing for  
50 each of six chosen index examples, comparing comorbid groups with prescribing levels in  
51 the respective index groups. Second, we wanted to test whether vascular comorbidity  
52 influenced key drug prescribing for chosen conditions. The vascular group were likely to  
53 be on similar multiple drugs, so the distinct hypothesis was tested, that was drug  
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3 prescribing in vascular conditions overall may influence key drug prescribing in the  
4 individual non-vascular conditions of COPD, OA or depression.  
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## 7 **Methods**

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10 **Design and Study population:** The cross-sectional study was conducted using two  
11 linked databases on patients aged 40 years and over presenting to general practice over  
12 a 2-year time period (from 1<sup>st</sup> January 2002 to 31<sup>st</sup> December 2003). We wanted to  
13 investigate what multi-drug prescribing levels were before a national UK performance-  
14 based incentive (Quality outcomes Framework) was implemented to test the associations  
15 between comorbidity and routine multi-drug prescribing. Ethical approval for the use of  
16 these anonymised databases was granted by the North Staffordshire Research Ethics  
17 Committee  
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23 **Settings:** The clinical and prescription databases analysed were derived from an  
24 anonymised computer recorded consultations from eleven general practices from the  
25 North Staffordshire Keele GP research partnership. The partnership covers a range of  
26 practices covering varying socioeconomic groups within rural and urban areas and has  
27 been involved in data collection over time for the purpose of epidemiological studies.  
28 There is an on-going process of data validation to improve data quality, and there is  
29 evidence that this measure improves data recording by general practitioners and their  
30 teams.<sup>23</sup>  
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36 **Chronic disease data:** The Consultation in Primary Care Archive (CiPCA) database  
37 focuses on the routinely collected morbidity encounters in actual consultations and coded  
38 using a standard clinical classification (Read codes).<sup>24</sup> Patients who had a record of a  
39 disease-specific READ coded morbidity of interest were included in the study and the  
40 main codes were used with all associated “daughter codes”. The main READ codes that  
41 were used to define the chronic disease groups were: diabetes mellitus (Read codes  
42 C10), cardiovascular diseases (ischaemic heart disease (G3); heart failure (G58),  
43 excluding hypertension)), cerebrovascular diseases (G6), chronic obstructive pulmonary  
44 disease (H30, excluding asthma) (COPD), osteoarthritis (N05, excluding arthralgia), and  
45 depression (E11, E20, Eu and excluding psychosis).  
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## 53 **Comorbidity: definitions**

54 There were two approaches to defining comorbidity. First, comorbidity was defined as the  
55 presence of one of the other five selected conditions. So using the diabetes population as  
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3 an example, the diabetes 'index' group was defined as diabetes 'alone' and without  
4 anyone of the other five conditions, whereas diabetes 'comorbid' group was defined as at  
5 least one of the other five conditions. The index 'alone' group would also enable the  
6 capture of the other morbidity that was outside of the ones within the study. This definition  
7 was applied to each of the six chronic conditions individually. Second, in the vascular  
8 group, comorbidity was defined separately as the individual and specific addition of  
9 COPD, OA or depression, and irrespective of whether the latter three occurred together.  
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### 14 15 **Prescribed drug measure: overall multi-drug count definitions**

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18 The Prescriptions in Primary Care Archive (PiPCA) database focuses on the routinely  
19 collected prescribed medications and which were coded using the British National  
20 Formulary (BNF) classification.<sup>25</sup> The BNF consists of 15 main chapters based on the  
21 systems of the body, and within which there are further sub-sections for specific clinical  
22 indications. Only patients on repeat drug prescriptions were selected for defining  
23 measures because this gives a better representation of multiple drugs used on a long  
24 term basis for the majority of patients with chronic conditions.  
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30 Specific drug treatment chapters for the six chronic diseases of interest in the study were  
31 identified and used as a summary of multi-drug counts. The BNF chapter for  
32 cardiovascular and cerebrovascular drugs were under BNF chapter 2, for COPD drugs  
33 under chapter 3, for depression under chapter 4, for diabetes mellitus under chapter 6,  
34 and for osteoarthritis under chapters 4 and 10. This means that overall; there were five  
35 main BNF chapters, which could constitute a measure of drug counts of up to a total of 5.  
36 The multi-drug count definition in this approach would then specifically relate to people  
37 prescribed drugs from at least two or more of the five chapters indicated.  
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### 43 44 **Vascular comorbidity and drug prescribing for non-vascular conditions**

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46 The key likelihood of receiving drug treatments for the specific conditions of COPD, OA  
47 and depression in the study population with vascular comorbidity was also investigated. In  
48 this approach the 'vascular' comorbidity was defined as the group any one of diabetes,  
49 cardiovascular disease and cerebrovascular disease. The non-vascular groups were then  
50 individually compared with and without vascular comorbidity. For example, the COPD  
51 group was compared with vascular comorbidity to the COPD without vascular comorbidity,  
52 in relation to the likelihood of receiving COPD-specific drug treatment.  
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3 Whilst the key drug treatments for COPD, OA and depression can be examined in  
4 different ways such as the use of specific drugs, or drug doses and duration of drug  
5 therapy, we wanted to first establish the simplest likelihood of a patient given any one of  
6 the key group of drugs for COPD, OA or depression. The group of drugs derived from  
7 guidelines for COPD<sup>10</sup> included bronchodilators, corticosteroids, inhaled steroids and  
8 oxygen(BNF sections 3.1, 3.2, 3.5 and 3.6). The group of drugs for osteoarthritis<sup>26</sup>  
9 included non-opioid analgesics, opioid analgesics, non-steroidal anti-inflammatories, and  
10 Cox 2 inhibitors (BNF sections 4.7.1, 4.7.2, 10.1.1 and 10.1.2.2). The group of drugs for  
11 depression<sup>11</sup> included hypnotics, anxiolytics and antidepressants (BNF sections 4.1 and  
12 4.3).

### 19 Analysis

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22 The first analyses was to describe the 2-year period prevalence of the 5 main BNF  
23 chapters in the specified chronic disease population, with a focus on some of the common  
24 drugs that were prescribed within each chapter expressed as drug prevalence/10,000  
25 population aged 40 years and over, and differences were assessed using Chi-square  
26 tests. The five main chapter drug categories prevalence are described by age, gender and  
27 deprivation status. Deprivation was measured by the Index of Multiple Deprivation (IMD)  
28 which is a composite score that is linked to postal address codes.<sup>27</sup> The IMD score was  
29 categorised into the bottom 20% (most deprived), middle 60% and the top 20% score  
30 (most affluent).

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33 For each of the six chronic conditions, associations between the comorbid groups and  
34 higher multi-drug counts were compared to the respective reference 'alone' group. The  
35 'outcome' of higher multi-drug therapy was defined as 3 or more of the chapter counts and  
36 compared to 2 counts or less. Associations using logistic regression were expressed as  
37 Odds Ratios (OR) with 95% confidence intervals (CI), and also included the ratios  
38 comparing prevalence of each drug count category in the comorbid group compared to  
39 the 'alone' group. Then for the vascular group, associations between each of the comorbid  
40 group with COPD, OA or depression were compared to the vascular 'alone' alone and  
41 higher multi-drug counts were then estimated.

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44 Finally, the data was analysed for the study defined optimal drug treatments for COPD,  
45 OA or depression. Three study groups constructed were: COPD and at least one of the  
46 vascular conditions; OA with at least one of the vascular conditions; and depression with  
47 at least one of the vascular conditions. Each group was the compared to their respective



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3 vascular group e.g. COPD and vascular group compared to COPD without a vascular  
4 condition, by the specific optimal drug treatment. Association estimates using logistic  
5 regression are presented both as unadjusted and adjusted figures with 95% confidence  
6 intervals. Analyses were carried out using SPSS version 17.0 statistical software.  
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## 10 **Results**

### 11 **Study population**

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15 In the study population of 12,875 aged 40 years and over, the number of patients  
16 prescribed with cardiovascular system drugs were 9,384 (2-year time-period prevalence  
17 73%), respiratory system drugs were 2,861 (22%), non-opioid analgesia were 5,395  
18 (42%), anti-depressants were 3,241 (25%), anti-diabetic drugs were 2,916 (23%) and  
19 musculoskeletal system anti-inflammatory drugs were 2143 (17%) (**Table 1**).  
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24 In terms of the socio-demographic distribution, older patients aged 70 years and over and  
25 populations in the top 20% most deprived status were significantly more likely to be  
26 prescribed all main drug categories, except for the cardiovascular system (Chi-square test  
27 for trend  $p < 0.001$ ). For women compared to men, there was variation by type of main drug  
28 category; the comparative 2-year prevalence figures by gender were significantly higher  
29 for men compared to women for the cardiovascular system drugs (76% vs 70%) and  
30 diabetes (26% vs 20%), but similar for COPD ( $p = 0.462$ ). Prevalence figures were lower  
31 for men compared to women for anxiolytics and anti-depressants (49% vs 66%) and anti-  
32 inflammatories (15% vs 18%) (Chi square test  $p < 0.001$  (**Table 2**)).  
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### 39 **Individual chronic condition comorbidity and higher multi-drug counts**

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42 For all six specified chronic conditions, at lower drugs counts of up to 2, the prevalence  
43 numbers were greater for the individual groups without the other five comorbid conditions  
44 compared to the numbers for the individual conditions with comorbidity of other five  
45 conditions (**Table 3**). For the drug count of 2 different chapters, the comorbid to 'alone'  
46 ratios ranged from 1.15 for the depression group to 0.5 for the diabetes group. The  
47 prevalence ratios were highest for the multi-drug count of 4, and these ranged from 13.7  
48 for the depression comorbid group to 2.3 for diabetes comorbid group.  
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54 Adjusting for age, gender and deprivation, the associations between the comorbid groups  
55 and higher multi-drug count compared to their respective 'alone' group ordered by  
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3 strength of association were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for  
4 depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for  
5 cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for  
6 diabetes, and OR 3.2 (2.6 to 4.0) for COPD.  
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### 10 **Vascular condition comorbidity and higher multi-drug counts**

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12 The prevalence ratios for the multi-drug count of 5 ranged from 3.9 for vascular group  
13 comorbid with osteoarthritis, to 1.9 for vascular group comorbid with COPD, and 1.0 for  
14 the vascular group comorbid with depression (**Table 4**). Adjusting for age, gender and  
15 deprivation, the associations between the comorbid groups and higher multi-group count  
16 compared to their respective 'alone' group ordered by strength of association were: Odds  
17 ratio 4.6 (95% Confidence Intervals 3.8 to 5.7) for vascular group comorbid with COPD,  
18 OR 3.2 (2.6 to 3.9) for vascular group comorbid with depression, and vascular group  
19 comorbid with OA OR 3.0 (2.6 to 3.5).  
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### 26 **Comorbid vascular conditions and optimal non-vascular condition prescribing**

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28 The three specific non-vascular groups of COPD, OA and depression were compared with  
29 comorbid vascular conditions to without such vascular comorbidity in terms of their  
30 respective optimal drug treatment (**Table 5**). Adjusting for age, gender and deprivation,  
31 the association between the COPD and vascular comorbid groups compared to their  
32 respective group without vascular conditions showed a significant reduction in optimal  
33 COPD drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.8).  
34 Adjusting for age, gender and deprivation, the association between the depression and  
35 vascular comorbid groups compared to their respective group without vascular conditions  
36 showed a significant reduction in optimal depression drug treatment with an Odds Ratio of  
37 0.6 (95% confidence interval 0.4 to 0.7). Adjusting for age, gender and deprivation, the  
38 association between the OA and vascular comorbid groups compared to their respective  
39 group without vascular conditions did not show a statistically significant reduction in  
40 optimal OA drug treatment with an Odds Ratio of 0.8 (95% confidence interval 0.6 to 1.1).  
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### 49 **Discussion**

50 Our findings from a large cross-sectional study of nearly 13,000 patients aged 40 years  
51 and over with one of six specified and common chronic conditions showed the scale of  
52 multi-drug prescribing, which was higher in the presence of comorbidity compared to the  
53 respective index groups. Whilst previous evidence has shown the high levels of multiple  
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3 drug prescribing<sup>15</sup>, our study findings link the disease status, comorbidity status to the  
4 measure of multi-drug prescribing for different systems.

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6 Depending on whether the chronic conditions were vascular (diabetes, cardiovascular or  
7 cerebrovascular) or non-vascular (COPD, OA or depression), the higher levels of multi-  
8 drug prescribing varied. All six conditions with comorbidity compared to their index  
9 condition had much higher multi-drug count, even adjusting for age, gender and  
10 deprivation. The measure of multi-drug count was notably distinct by the use of five  
11 different main drug chapter categories which were for different body systems, which  
12 means that this 'outcome' was not about multiple drugs use for the same condition. For  
13 example, a diabetic with a higher multi-drug count of 4 or 5 in this study relates to different  
14 and distinct body systems, and not to the different drugs under the same chapter. The  
15 chronic condition of depression comorbidity had the strongest strength of association with  
16 higher multi-drug counts, followed by cardiovascular disease comorbidity, and the  
17 estimates of association for cerebrovascular disease, osteoarthritis and diabetes were  
18 similar. These findings suggest that the index condition and comorbidity may influence the  
19 range of multi-drug prescribing, and generates the interesting hypothesis on the potential  
20 variation in clinical outcomes of the index conditions may be because of underlying  
21 comorbid drug prescribing.

22  
23 The study also grouped the vascular-related conditions to investigate the influence of non-  
24 vascular drug prescribing compared to vascular conditions 'alone' (i.e. without any one of  
25 COPD, OA or depression). Again, the adjusted associations were significant, with  
26 vascular comorbidity being associated with higher-multi-drug counts compared to the  
27 respective 'vascular index' group. Here the clinical implication is that vascular comorbidity  
28 in populations aged 40 years and over might not only be associated with multiple vascular  
29 drugs as routinely suggested by clinical guidelines<sup>28</sup>, but by a range of conditions such as  
30 comorbidity of COPD, OA or depression. It is possible that these conditions and the drug  
31 treatments for them may also in the end influence the health and healthcare outcomes of  
32 the index vascular conditions.<sup>29</sup>

33  
34 In terms of the influence of comorbidity on key drug prescribing, our study findings show  
35 that vascular comorbidity in COPD and depression is associated with lower likelihood of  
36 drug prescribing for the respective conditions of COPD and depression. Similar findings,  
37 particularly for sub-optimal depression drug treatment, when depression is comorbid with  
38 chronic disease have been shown previously.<sup>30,31</sup> However, such findings for osteoarthritis  
39 were not found, and here it is possible that the study definition of analgesia was too broad,  
40 as analgesia use covers a range of other painful conditions, in addition to osteoarthritis.

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42 Although the key drug definition was simple and broad, our study findings seem to

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3 suggest that comorbidity does influence drug prescribing for specific conditions. Whether  
4 this is due to some kind of therapeutic inertia or is due to GPs' reasoned consideration of  
5 drug-drug and drug-disease interactions and the overall well-being of the patient is the  
6 important question raised by the findings.  
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11 The approach taken to looking at specific groups and six common conditions was based  
12 on a combination of clinical rationale and feasibility. Whilst, one could have investigated  
13 any number of combinations of the six conditions, the better and preferred approach taken  
14 was to group conditions first at the "vascular" level. As highlighted earlier, diabetes,  
15 ischaemic heart disease and cerebrovascular disease have shared pathogenesis and  
16 there may be over-lapping of drug treatments. However, the "non-vascular" group  
17 constitute individual chronic conditions with distinct and un-related drug treatments. This  
18 approach enabled comorbidity definitions based on (i) group-level i.e. vascular  
19 comorbidity with one of the non-vascular conditions and (ii) counts i.e. number of other  
20 conditions for each of the six index groups. The study focus was also on comorbidity and  
21 further research is also required on how multimorbidity, defined as two or more conditions,  
22 influences the overall prescribing of multiple drugs and when the unit of analysis for  
23 outcome is not the disease but the arguably more important patient-centred outcomes.  
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32 The large scale study of specified chronic diseases was conducted using an anonymised  
33 database for a 2-year time-period. In terms of the cross-sectional associations, the  
34 findings on the levels of chronic conditions, comorbidity and multi-drug prescribing do offer  
35 clinical implications as outlined earlier. However, the implications of the associations  
36 between comorbidity and the key drug definitions may be limited in this cross-sectional  
37 design and these may be treated cautiously as emergent findings. The chronic disease  
38 definitions were also based on routinely collected registers from general practices, which  
39 were and are part of a research network dedicated to the collection of clinical data in  
40 actual consultation. Whilst these chronic disease registers may be subject to variations in  
41 recording<sup>32</sup>, the study analyses provide the estimates of association in actual clinical  
42 practice across 11 different sites.  
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49 The drug definitions were based on routinely coded repeat prescriptions and over a 2-year  
50 time-period represent an appropriate measure at the simpler but distinct broad system  
51 category. Patients however will also have been prescribed other drug categories outside  
52 of the five main categories that we had selected and for other less common conditions  
53 from the ones selected in the study, which means these drug levels are a specific  
54 estimate. The construction of our study defined index or 'alone' groups (without the other  
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3 5 conditions) provided the relative multi-drug level estimates to when the index condition  
4 was comorbid with one of the other 5 conditions. So the multi-drug levels in the 'alone'  
5 group provide an estimate of main drug system prescribing without the associated  
6 condition (i.e. for other indications) compared to levels when there is a clear comorbidity  
7 record. However, this is time-defined by a 2-year time window, so some mis-classification  
8 may be possible and further research could explore how broad system drug definitions  
9 capture the underlying and specific common diagnostic categories. Further research is  
10 also required for the arguably more complex assimilation of the range of defined drug  
11 categories, other multi-morbidity and to investigate specific effect of individual drugs  
12 categories. Most of these drugs, other than analgesia such as anti-inflammatories, are not  
13 available over the counter and are usually clinician prescribed. So it is possible that  
14 common over the counter drugs, particularly in relation to osteoarthritis, may be an under-  
15 estimate; however, the selection of repeated prescribing would mitigate against such  
16 under-estimation. Finally, although a large scale study, these general practices are drawn  
17 from one region of England, and whilst this might limit generalisability, the internal validity  
18 of the findings still remains.

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21 In conclusion, our study findings show the links between common chronic conditions,  
22 comorbidity and associated multi-drug prescribing. The key and distinct finding is that the  
23 study shows that multi-drug prescribing defined by a range of selected but different  
24 systems is high in chronic conditions and higher in comorbidity. The common group of  
25 vascular conditions are not the only ones associated with their 'own' guideline driven  
26 multi-drug therapy, but the addition of non-vascular conditions such as COPD, OA and  
27 depression adds to the multi-drugs burden in patients. The importance of these findings,  
28 in addition to quantifying the scale, is whether such multi-drug therapy influences the  
29 quality of care for each of the individual conditions. Our findings suggest the potential for  
30 sub-optimal drug treatment as a consequence is in line with other evidence<sup>33</sup>, but further  
31 research is required to investigate the impact of disease status, comorbidity, multi-drug  
32 therapy on prospective and long-term outcomes of clinical care.  
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**Data sharing:** Data is not available for sharing under existing governance arrangements and no additional data is available.

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**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 <sup>†</sup>
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	Beta 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	n/a	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 anti-diabetic 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

<sup>†</sup>Population refers to those with one of six chronic conditions ( $n = 12875$ ), which included hypertension, diabetes, coronary heart disease, cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD), osteoarthritis (OA) and depression; Drug categories are based on the British National Formulary (BNF) classification

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**Table 2: Socio-demographic characteristics of the main drug categories**

Factor	Total Numbers	Main drug categories				Musculo-skeletal System
		Cardiovascular system	Respiratory System	Central-nervous System	Endocrine System	
<b>Age (years)</b>						
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 years and over	715	608 (85)	135 (19)	513 (72)	101 (14)	59 (8)
<b>Gender</b>						
Women	6896	4813 (70)	1510 (22)	4528 (66)	1351 (20)	1260 (18)
Men	5979	4571 (76)	1351 (23)	2950 (49)	1565 (26)	883 (15)
<b>Deprivation**</b>						
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 sub-group*

**Table 3: Associations between individual study groups and higher multi-drug counts**

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (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 (3.0-4.2)
<i>Prevalence ratio</i>	<i>0.2</i>	<i>0.4</i>	<i>0.5</i>	<i>1.5</i>	<i>2.3</i>	<i>3.3</i>	
CHD 'alone'	148	4057	4248	1372	160	16	1.0
CHD comorbidity	36	1027	3973	3516	1327	121	5.35 (4.6-6.3)
<i>Prevalence ratio</i>	<i>0.2</i>	<i>0.3</i>	<i>0.9</i>	<i>2.6</i>	<i>8.3</i>	<i>7.6</i>	
CVD 'alone'	688	4087	3848	1306	70	0	1.0
CVD comorbidity	41	1745	4251	3224	678	62	3.70 (2.8-5.0)
<i>Prevalence ratio</i>	<i>0.1</i>	<i>0.4</i>	<i>1.1</i>	<i>2.5</i>	<i>9.7</i>	<i>n/a</i>	
COPD 'alone'	940	2487	3496	2726	350	0	1.0
COPD comorbidity	189	946	2855	4117	1751	142	3.22 (2.6-4.0)
<i>Prevalence ratio</i>	<i>0.20</i>	<i>0.4</i>	<i>0.8</i>	<i>1.5</i>	<i>5.00</i>	<i>n/a</i>	
OA 'alone'	1378	2786	3722	1854	256	5	1.0
OA comorbidity	174	1260	3550	3420	1325	271	3.64 (3.1-4.3)
<i>Prevalence ratio</i>	<i>0.1</i>	<i>0.5</i>	<i>1.0</i>	<i>1.8</i>	<i>5.2</i>	<i>54</i>	
Depression 'alone'	1912	4140	3093	776	79	0	1.0
Depression comorbidity	325	1422	3555	3555	1082	62	7.11 (5.6-9.0)
<i>Prevalence ratio</i>	<i>0.17</i>	<i>0.34</i>	<i>1.15</i>	<i>4.58</i>	<i>13.7</i>	<i>n/a</i>	

\*Alone – people with disease alone and none of the other 5 morbidities, comorbidity is 1 or more of other 5 study morbidities, \*\*Comorbid drug 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 to 4 combined) compared to lower drug counts (2 or less), CHD is coronary heart disease and CVD is cerebro-vascular disease

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**Table 4: Associations between vascular comorbidity groups and higher multi-drug counts**

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (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 (3.8-5.7)
<i>Prevalence ratio</i>	<i>0.43</i>	<i>0.29</i>	<i>0.71</i>	<i>1.65</i>	<i>2.60</i>	<i>1.90</i>	
Vascular group and OA	29	873	3493	3697	1557	349	3.01 (2.6-3.5)
<i>Prevalence ratio</i>	<i>0.15</i>	<i>0.37</i>	<i>0.87</i>	<i>1.45</i>	<i>2.01</i>	<i>3.92</i>	
Vascular group and Depression	69	829	3733	3917	1359	92	3.22 (2.6-3.9)
<i>Prevalence ratio</i>	<i>0.35</i>	<i>0.35</i>	<i>0.93</i>	<i>1.54</i>	<i>1.76</i>	<i>1.03</i>	

\*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 to 4 combined) compared to lower drug counts (2 or less)

**Table 5: Key drug treatment of non-vascular conditions in vascular comorbidity**

Numbers (%)	Key drug treatments		Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (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 (0.43-0.78)	0.55 (0.40-0.75)
OA without vascular comorbidity	281 (16)	1440 (84)	1.0	1.0
OA and vascular comorbidity	117 (17)	568 (83)	0.95 (0.75-1.20)	0.82 (0.64-1.06)
Depression without vascular comorbidity	259 (16)	1378 (84)	1.0	1.0
Depression and vascular group	120 (28)	311 (72)	0.49 (0.38-0.62)	0.55 (0.42-0.73)

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



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For peer review only

**Title: Chronic condition comorbidity and multi-drug therapy in general practice  
populations: a cross-sectional linkage study**

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*Key words: co-morbidity; drug therapy; chronic disease; depression; epidemiology*

*Main text count: 3898*

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3 *Abstract*  
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5 **Objectives:** The study investigated (i) the association between comorbidity and multi-drug  
6 prescribing compared to the index condition, and (ii) the association between vascular  
7 comorbidity and non-vascular condition optimal-key drug prescribing.  
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10 **Design:** Cross-sectional study linking anonymised computer consultations with  
11 prescription records for a 2-year time-period.  
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13 **Setting:** 11 general practices in North Staffordshire, England.  
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15 **Participants:** Study groups aged 40 years and over (N=12,875). Within six conditions,  
16 comorbid group with the other 5 conditions was compared to an 'alone' group without  
17 them. Additionally how the 'vascular' (one of diabetes, cardiovascular disease and  
18 cerebrovascular disease) comorbidity influenced COPD, OA or depression drug  
19 prescribing was investigated.  
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22 **Outcome Measures:** Based on the British National Formulary, five main drug chapters  
23 constituted a measure of drug counts, with low count as 2 or less and high multi-drug  
24 count as 3 or more. Key drugs prescribed for COPD, OA and depression were derived  
25 from guidelines.  
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28 **Results:** The adjusted associations between the comorbid groups and higher multi-drug  
29 count compared to their respective 'alone' group were: Odds ratio 7.1 (95% Confidence  
30 Intervals 5.6 to 9.0) for depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7  
31 (2.8 to 5.0) for cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0  
32 to 4.2) for diabetes, and OR 3.2 (2.6 to 4.0) for COPD.  
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35 In COPD, vascular comorbidity was associated with a significant reduction in key COPD  
36 drug treatments (adjusted Odds Ratio 0.6 (95% confidence interval 0.4 to 0.8). In  
37 depression, vascular comorbidity was associated with a reduction in key depression drug  
38 treatments (OR 0.6 (0.4 to 0.7)).  
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41 **Conclusions:** Our findings show multi-drug prescribing for different body systems is  
42 higher with comorbidity and may be associated with lower likelihood of prescribing for  
43 specific conditions. Further research is required on whether multi-drug prescribing  
44 influences the outcomes of care for chronic conditions.  
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## Article summary

### *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 multi-drug measurement which accounts for vascular condition-specific drugs as well as summarising non-vascular co-drug therapy.
- The study provides the emergent approach to investigating the influence of multi-drug 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 multi-drug 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 multi-drug 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.<sup>1,2</sup> 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, have shown that this phenomenon is associated with adverse health, increased health care utilisation and increased mortality.<sup>3,4,5</sup> 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.<sup>6,7</sup>

Many national health care 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.<sup>8,9,10,11,12</sup> 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.<sup>13</sup> 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 (i) how does multiple drug prescribing for different systems relate to the primary index condition and (ii) how does multiple drug prescribing escalate when populations experience multiple conditions which might be directly linked or occur by chance together. The cardio-metabolic 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 patho-physiology. For example, other common chronic conditions include chronic obstructive airways disease and

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3 depression, and this epidemiology provides the scale of multiple drug therapies when co-  
4 occurring conditions might be un-related.  
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8 In terms of the current evidence in this field, much of it has focused around  
9 'polypharmacy' studies.<sup>14,15,16</sup> However, whilst this might seem an appropriate broad  
10 umbrella term, in research and clinical approaches, it has often focused on arbitrarily  
11 chosen number of drugs, and linked the term to either inappropriate prescribing or  
12 associated adverse events in older populations.<sup>16</sup> This lack of consensus defined  
13 approach to this problem has led to an argument for less ambiguous terminology<sup>17</sup>, and  
14 we propose that 'multi-drug' therapy is used to link in with the standard approach to two or  
15 more conditions, which is 'multi-morbidity'. Within this evidence, there is still a clear gap in  
16 how morbidity link to drug prescribing, and whether comorbidity influences the drug  
17 prescribing for an index disease.  
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24 In this study, the focus was on six common chronic conditions in the general population,  
25 which included diabetes mellitus, cardiovascular diseases, cerebrovascular diseases  
26 chronic obstructive pulmonary diseases, osteoarthritis and depression. The choice of  
27 these chronic conditions for the purpose of the study was based on a number of factors  
28 including the epidemiology, especially prevalence of the diseases, as well as aetio-  
29 pathogenesis and impacts on quality of life and psychological well-being. For example,  
30 while diabetes mellitus, coronary heart disease and cerebrovascular diseases have a  
31 common pathological basis of causation (the 'vascular group'), and often co-exist in one  
32 patient, they are also known to have high mortality rates - hence the drive towards  
33 measures aimed at optimising the management of these diseases.<sup>18,19</sup> The other three,  
34 non-vascular chronic conditions - chronic obstructive pulmonary disease (COPD),  
35 osteoarthritis (OA) and depression are leading causes of morbidity, high cost of care and  
36 psychological distress respectively.<sup>20,21,22</sup> The rationale for our focus on few selected  
37 common conditions was also to provide common comorbidity combinations which are  
38 potentially treated with drugs as a key intervention.  
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48 We investigated two separate issues using the selected group of vascular and non-  
49 vascular conditions. First, we wanted to investigate the relative multi-drug prescribing for  
50 each of six chosen index examples, comparing comorbid groups with prescribing levels in  
51 the respective index groups. Second, we wanted to test ~~of~~ whether vascular comorbidity  
52 influenced key drug prescribing for chosen conditions. The vascular group were likely to  
53 be on similar multiple drugs, so the distinct hypothesis was tested, that was drug  
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3 prescribing in vascular conditions overall may influence key drug prescribing in the  
4 individual non-vascular conditions of COPD, OA or depression.  
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## 7 **Methods**

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10 **Design and Study population:** The cross-sectional study was conducted using two  
11 linked databases on patients aged 40 years and over presenting to general practice over  
12 a 2-year time period (from 1<sup>st</sup> January 2002 to 31<sup>st</sup> December 2003). We wanted to  
13 investigate what multi-drug prescribing levels were before a national UK performance-  
14 based incentive (Quality outcomes Framework) was implemented to test the associations  
15 between comorbidity and routine multi-drug prescribing. Ethical approval for the use of  
16 these anonymised databases was granted by the North Staffordshire Research Ethics  
17 Committee  
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23 **Settings:** The clinical and prescription databases analysed were derived from an  
24 anonymised computer recorded consultations from eleven general practices from the  
25 North Staffordshire Keele GP research partnership. The partnership covers a range of  
26 practices covering varying socioeconomic groups within rural and urban areas and has  
27 been involved in data collection over time for the purpose of epidemiological studies.  
28 There is an on-going process of data validation to improve data quality, and there is  
29 evidence that this measure improves data recording by general practitioners and their  
30 teams.<sup>23</sup>  
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36 **Chronic disease data:** The Consultation in Primary Care Archive (CiPCA) database  
37 focuses on the routinely collected morbidity encounters in actual consultations and coded  
38 using a standard clinical classification (Read codes).<sup>24</sup> Patients who had a record of a  
39 disease-specific READ coded morbidity of interest were included in the study and the  
40 main codes were used with all associated “daughter codes”. The main READ codes that  
41 were used to define the chronic disease groups were: diabetes mellitus (Read codes  
42 C10), cardiovascular diseases (ischaemic heart disease (G3); heart failure (G58),  
43 excluding hypertension)), cerebrovascular diseases (G6), chronic obstructive pulmonary  
44 disease (H30, excluding asthma) (COPD), osteoarthritis (N05, excluding arthralgia), and  
45 depression (E11, E20, Eu and excluding psychosis).  
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## 53 **Comorbidity: definitions**

54 There were two approaches to defining comorbidity. First, comorbidity was defined as the  
55 presence of one of the other five selected conditions. So using the diabetes population as  
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3 an example, the diabetes 'index' group was defined as diabetes 'alone' and without  
4 anyone of the other five conditions, whereas diabetes 'comorbid' group was defined as at  
5 least one of the other five conditions. The index 'alone' group would also enable the  
6 capture of the other morbidity that was outside of the ~~study-selected conditions~~ ones within  
7 the study. This definition was applied to each of the six chronic conditions individually.  
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11 Second, in the vascular group, comorbidity was defined separately as the individual and  
12 specific addition of COPD, OA or depression, and irrespective of whether the latter three  
13 occurred together.  
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### 15 16 17 **Prescribed drug measure: overall multi-drug count definitions**

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19 The Prescriptions in Primary Care Archive (PiPCA) database focuses on the routinely  
20 collected prescribed medications and which were coded using the British National  
21 Formulary (BNF) classification.<sup>25</sup> The BNF consists of 15 main chapters based on the  
22 systems of the body, and within which there are further sub-sections for specific clinical  
23 indications. Only patients on repeat drug prescriptions were selected for defining  
24 measures because this gives a better representation of multiple drugs used on a long  
25 term basis for the majority of patients with chronic conditions.  
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31 Specific drug treatment chapters for the six chronic diseases of interest in the study were  
32 identified and used as a summary of multi-drug counts. The BNF chapter for  
33 cardiovascular and cerebrovascular drugs were under BNF chapter 2, for COPD drugs  
34 under chapter 3, for depression under chapter 4, for diabetes mellitus under chapter 6,  
35 and for osteoarthritis under chapters 4 and 10. This means that overall; there were five  
36 main BNF chapters, which could constitute a measure of drug counts of up to a total of 5.  
37 The multi-drug count definition in this approach would then specifically relate to people  
38 prescribed drugs from at least two or more of the five chapters indicated.  
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### 44 45 **Vascular comorbidity and drug prescribing for non-vascular conditions**

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47 The key likelihood of receiving drug treatments for the specific conditions of COPD, OA  
48 and depression in the study population with vascular comorbidity was also investigated. In  
49 this approach the 'vascular' comorbidity was defined as the group any one of diabetes,  
50 cardiovascular disease and cerebrovascular disease. The non-vascular groups were then  
51 individually compared with and without vascular comorbidity. For example, the COPD  
52 group was compared with vascular comorbidity to the COPD without vascular comorbidity,  
53 in relation to the likelihood of receiving COPD-specific drug treatment.  
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3 Whilst the key drug treatments for COPD, OA and depression can be examined in  
4 different ways such as the use of specific drugs, or drug doses and duration of drug  
5 therapy, we wanted to first establish the simplest likelihood of a patient given any one of  
6 the key group of drugs for COPD, OA or depression. The group of drugs derived from  
7 guidelines for COPD<sup>10</sup> included bronchodilators, corticosteroids, inhaled steroids and  
8 oxygen(BNF sections 3.1, 3.2, 3.5 and 3.6). The group of drugs for osteoarthritis<sup>26</sup>  
9 included non-opioid analgesics, opioid analgesics, non-steroidal anti-inflammatories, and  
10 Cox 2 inhibitors (BNF sections 4.7.1, 4.7.2, 10.1.1 and 10.1.2.2). The group of drugs for  
11 depression<sup>11</sup> included hypnotics, anxiolytics and antidepressants (BNF sections 4.1 and  
12 4.3).

### 19 Analysis

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22 The first analyses was to describe the 2-year period prevalence of the 5 main BNF  
23 chapters in the specified chronic disease population, with a focus on some of the common  
24 drugs that were prescribed within each chapter expressed as drug prevalence/10,000  
25 population aged 40 years and over, and differences were assessed using Chi-square  
26 tests. The five main chapter drug categories prevalence are described by age, gender and  
27 deprivation status. Deprivation was measured by the Index of Multiple Deprivation (IMD)  
28 which is a composite score that is linked to postal address codes.<sup>27</sup> The IMD score was  
29 categorised into the bottom 20% (most deprived), middle 60% and the top 20% score  
30 (most affluent).

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33 For each of the six chronic conditions, associations between the comorbid groups and  
34 higher multi-drug counts were compared to the respective reference 'alone' group. The  
35 'outcome' of higher multi-drug therapy was defined as 3 or more of the chapter counts and  
36 compared to 2 counts or less. Associations using logistic regression were expressed as  
37 Odds Ratios (OR) with 95% confidence intervals (CI), and also included the ratios  
38 comparing prevalence of each drug count category in the comorbid group compared to  
39 the 'alone' group. Then for the vascular group, associations between each of the comorbid  
40 group with COPD, OA or depression were compared to the vascular 'alone' alone and  
41 higher multi-drug counts were then estimated.

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44 Finally, the data was analysed for the study defined optimal drug treatments for COPD,  
45 OA or depression. Three study groups constructed were: COPD and at least one of the  
46 vascular conditions; OA with at least one of the vascular conditions; and depression with  
47 at least one of the vascular conditions. Each group was the compared to their respective

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3 vascular group e.g. COPD and vascular group compared to COPD without a vascular  
4 condition, by the specific optimal drug treatment. Association estimates using logistic  
5 regression are presented both as unadjusted and adjusted figures with 95% confidence  
6 intervals. Analyses were carried out using SPSS version 17.0 statistical software.  
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## 10 Results

### 11 Study population

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13 In the study population of 12,875 aged 40 years and over, the number of patients  
14 prescribed with cardiovascular system drugs were 9,384 (2-year time-period prevalence  
15 73%), respiratory system drugs were 2,861 (22%), non-opioid analgesia were 5,395  
16 (42%), anti-depressants were 3,241 (25%), anti-diabetic drugs were 2,916 (23%) and  
17 musculoskeletal system anti-inflammatory drugs were 2143 (17%) (Table 1).  
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24 In terms of the socio-demographic distribution, older patients aged 70 years and over and  
25 populations in the top 20% most deprivation-deprived status were significantly more likely  
26 to be prescribed all main drug categories, except for the cardiovascular system (Chi-  
27 square test for trend  $p < 0.001$ ). For women compared to men, there was variation by type  
28 of main drug category; the comparative 2-year prevalence figures by gender were  
29 significantly higher for men compared to women for the cardiovascular system drugs (76%  
30 vs 70%) and diabetes (26% vs 20%), but similar for COPD ( $p = 0.462$ ). Prevalence figures  
31 were lower for men compared to women for anxiolytics and anti-depressants (49% vs  
32 66%) and anti-inflammatories (15% vs 18%) (Chi square test  $p < 0.001$  (Table 2)).  
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### 39 Individual chronic condition comorbidity and higher multi-drug counts

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41 For all six specified chronic conditions, at lower drugs counts of up to 2, the prevalence  
42 numbers were greater for the individual groups without the other five comorbid conditions  
43 compared to the numbers for the individual conditions with comorbidity of other five  
44 conditions (Table 3). For the drug count of 2 different chapters, the comorbid to 'alone'  
45 ratios ranged from 1.15 for the depression group to 0.5 for the diabetes group. The  
46 prevalence ratios were highest for the multi-drug count of 4, and these ranged from 13.7  
47 for the depression comorbid group to 2.3 for diabetes comorbid group.  
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54 Adjusting for age, gender and deprivation, the associations between the comorbid groups  
55 and higher multi-group-drug count compared to their respective 'alone' group ordered by  
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3 strength of association were: Odds ratio 7.1 (95% Confidence Intervals 5.6 to 9.0) for  
4 depression, OR 5.4 (4.6 to 6.3) for cardiovascular disease, OR 3.7 (2.8 to 5.0) for  
5 cerebrovascular disease, OR 3.6 (3.1 to 4.3) for osteoarthritis, OR 3.5 (3.0 to 4.2) for  
6 diabetes, and OR 3.2 (2.6 to 4.0) for COPD.  
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### 10 **Vascular condition comorbidity and higher multi-drug counts**

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12 The prevalence ratios for the multi-drug count of 5 ranged from 3.9 for vascular group  
13 comorbid with osteoarthritis, to 1.9 for vascular group comorbid with COPD, and 1.0 for  
14 the vascular group comorbid with depression (**Table 4**). Adjusting for age, gender and  
15 deprivation, the associations between the comorbid groups and higher multi-group count  
16 compared to their respective 'alone' group ordered by strength of association were: Odds  
17 ratio 4.6 (95% Confidence Intervals 3.8 to 5.7) for vascular group comorbid with COPD,  
18 OR 3.2 (2.6 to 3.9) for vascular group comorbid with depression, and vascular group  
19 comorbid with OA OR 3.0 (2.6 to 3.5).  
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### 26 **Comorbid vascular conditions and optimal non-vascular condition prescribing**

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28 The three specific non-vascular groups of COPD, OA and depression were compared with  
29 comorbid vascular conditions to without such vascular comorbidity in terms of their  
30 respective optimal drug treatment (**Table 5**). Adjusting for age, gender and deprivation,  
31 the association between the COPD and vascular comorbid groups compared to their  
32 respective group without vascular conditions showed a significant reduction in optimal  
33 COPD drug treatment with an Odds Ratio of 0.6 (95% confidence interval 0.4 to 0.8).  
34 Adjusting for age, gender and deprivation, the association between the depression and  
35 vascular comorbid groups compared to their respective group without vascular conditions  
36 showed a significant reduction in optimal depression drug treatment with an Odds Ratio of  
37 0.6 (95% confidence interval 0.4 to 0.7). Adjusting for age, gender and deprivation, the  
38 association between the OA and vascular comorbid groups compared to their respective  
39 group without vascular conditions did not show a statistically significant reduction in  
40 optimal OA drug treatment with an Odds Ratio of 0.8 (95% confidence interval 0.6 to 1.1).  
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### 49 **Discussion**

50 Our findings from a large cross-sectional study of nearly 13,000 patients aged 40 years  
51 and over with one of six specified and common chronic conditions showed the scale of  
52 multi-drug prescribing, which was higher in the presence of comorbidity compared to the  
53 respective index groups. Whilst previous evidence has shown the high levels of multiple  
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3 drug prescribing<sup>15</sup>, our study findings link the disease status, comorbidity status to the  
4 measure of multi-drug prescribing for different systems.

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6 Depending on whether the chronic conditions were vascular (diabetes, cardiovascular or  
7 cerebrovascular) or ~~the~~ non-vascular (COPD, OA or depression), the higher levels of  
8 multi-drug prescribing varied. All six conditions with comorbidity compared to their index  
9 condition had much higher multi-drug count, even adjusting for age, gender and  
10 deprivation. The measure of multi-drug count was notably distinct by the use of five  
11 different main drug chapter categories which were for different body systems, which  
12 means that this 'outcome' was not about multiple drugs use for the same condition. For  
13 example, a diabetic with a higher multi-drug count of 4 or 5 in this study relates to different  
14 and distinct body systems, and not to the different drugs under the same chapter. The  
15 chronic condition of depression comorbidity had the strongest strength of association with  
16 higher multi-drug counts, followed by cardiovascular disease comorbidity, and the  
17 estimates of association for cerebrovascular disease, osteoarthritis and diabetes were  
18 similar. These findings suggest that the index condition and comorbidity may influence the  
19 range of multi-drug prescribing, and generates the interesting hypothesis on the potential  
20 variation in clinical outcomes of the index conditions may be because of underlying  
21 comorbid drug prescribing.

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23 The study also grouped the vascular-related conditions to investigate the influence of non-  
24 vascular drug prescribing compared to vascular conditions 'alone' (i.e. without any one of  
25 COPD, OA or depression). Again, the adjusted associations were significant, with  
26 vascular comorbidity being associated with higher-multi-drug counts compared to the  
27 respective 'vascular index' group. Here the clinical implication is that vascular comorbidity  
28 in populations aged 40 years and over might not only be associated with multiple vascular  
29 drugs as routinely suggested by clinical guidelines<sup>28</sup>, but by a range of conditions such as  
30 comorbidity of COPD, OA or depression. It is possible that these conditions and the drug  
31 treatments for them may also in the end influence the health and healthcare outcomes of  
32 the index vascular conditions.<sup>29</sup>

33  
34 In terms of the influence of comorbidity on key drug prescribing, our study findings show  
35 that vascular comorbidity in COPD and depression is associated with lower likelihood of  
36 drug prescribing for the respective conditions of COPD and depression. Similar findings,  
37 particularly for sub-optimal depression drug treatment, when depression is comorbid with  
38 chronic disease ~~has~~ have been shown previously.<sup>30,31</sup> However, such findings for  
39 osteoarthritis were not found, and here it is possible that the 'outcome' study definition of  
40 analgesia was too broad, as analgesia use covers a range of other painful conditions, in  
41 addition to osteoarthritis. Although the key drug definition was simple and broad, our study

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3 findings seem to suggest that comorbidity does influence drug prescribing for specific  
4 conditions. Whether this is due to some kind of therapeutic inertia or is due to GPs'  
5 reasoned consideration of drug-drug and drug-disease interactions and the overall well-  
6 being of the patient is the important question raised by the findings.  
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11 The approach taken to looking at specific groups and six common conditions was based  
12 on a combination of clinical rationale and feasibility. Whilst, one could have investigated  
13 any number of combinations of the six conditions, the better and preferred approach taken  
14 was to group conditions first at the "vascular" level. As highlighted earlier, diabetes,  
15 ischaemic heart disease and cerebrovascular disease have shared pathogenesis and  
16 there may be over-lapping of drug treatments. However, the "non-vascular" group  
17 constitute individual chronic conditions with distinct and un-related drug treatments. This  
18 approach enabled comorbidity definitions based on (i) group-level i.e. vascular  
19 comorbidity with one of the non-vascular conditions and (ii) counts i.e. number of other  
20 conditions for each of the six index groups. The study focus was also on comorbidity and  
21 further research is also required on how multimorbidity, defined as two or more conditions,  
22 influences the overall prescribing of multiple drugs and when the unit of analysis for  
23 outcome is not the disease but the arguably more important patient-centred outcomes.  
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32 The large scale study of specified chronic diseases was conducted using an anonymised  
33 database for a 2-year time-period. In terms of the cross-sectional associations, the  
34 findings on the levels of chronic conditions, comorbidity and multi-drug prescribing do offer  
35 clinical implications as outlined earlier. However, the implications of the associations  
36 between comorbidity and the key drug definitions may be limited in this cross-sectional  
37 design and these may be treated cautiously as emergent findings. The chronic disease  
38 definitions were also based on routinely collected registers from general practices, which  
39 were and are part of a research network dedicated to the collection of clinical data in  
40 actual consultation. Whilst these chronic disease registers may be subject to variations in  
41 recording<sup>32</sup>, the study analyses provide the estimates of association in actual clinical  
42 practice across 11 different sites.  
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49 The drug definitions were based on routinely coded repeat prescriptions and over a 2-year  
50 time-period represent an appropriate measure at the simpler but distinct broad system  
51 category. Patients however will also have been prescribed other drug categories outside  
52 of the five main categories that we had selected and for other less common conditions  
53 from the ones selected in the study, which means these drug levels are a specific  
54 estimate. The construction of our study defined index or 'alone' groups (without the other  
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3 5 conditions) provided the relative multi-drug level estimates to when the index condition  
4 was comorbid with one of the other 5 conditions. So the multi-drug levels in the 'alone'  
5 group provide an estimate of main drug system prescribing without the associated  
6 condition (i.e. for other indications) compared to levels when there is a clear comorbidity  
7 record. However, this is time-defined by a 2-year time window, so some mis-classification  
8 may be possible and further research could explore how broad system drug definitions  
9 capture the underlying and specific common diagnostic categories. Further research is  
10 also required for the arguably more complex assimilation of the range of defined drug  
11 categories, other multi-morbidity and to investigate specific effect of individual drugs  
12 categories. Most of these drugs, other than analgesia such as anti-inflammatories, are not  
13 available over the counter and are usually clinician prescribed. So it is possible that  
14 common over the counter drugs, particularly in relation to osteoarthritis, may be an under-  
15 estimate; however, the selection of repeated prescribing would mitigate against such  
16 under-estimation. Finally, although a large scale study, these general practices are drawn  
17 from one region of England, and whilst this might limit generalisability, the internal validity  
18 of the findings still remains.

19  
20 In conclusion, our study findings show the links between common chronic conditions,  
21 comorbidity and associated multi-drug prescribing. The key and distinct finding is that the  
22 study shows that multi-drug prescribing defined by a range of selected but different  
23 systems is high in chronic conditions and higher in comorbidity. The common group of  
24 vascular conditions are not the only ones associated with their 'own' guideline driven  
25 multi-drug therapy, but the addition of non-vascular conditions such as COPD, OA and  
26 depression adds to the multi-drugs burden in patients. The importance of these findings,  
27 in addition to quantifying the scale, is whether such multi-drug therapy influences the  
28 quality of care for each of the individual conditions. Our findings suggest the potential for  
29 sub-optimal drug treatment as a consequence is in line with other evidence<sup>33</sup>, but further  
30 research is required to investigate the impact of disease status, comorbidity, multi-drug  
31 therapy on prospective and long-term outcomes of clinical care.  
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**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 <sup>†</sup>
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	Beta 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	n/a	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 anti-diabetic drugs	Metformin, Gliclazide	2334	1805



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10 Musculoskeletal and joint disease			2143	1664
10.1.1	Non-steroidal anti-inflammatory drugs	Ibuprofen, cyclooxygenase inhibitors	2143	1664

<sup>†</sup>Population refers to those with one of six chronic conditions (n = 12875), which included hypertension, diabetes, coronary heart disease, cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD), osteoarthritis (OA) and depression; Drug categories are based on the British National Formulary (BNF) classification

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Table 2: Socio-demographic characteristics of the main drug categories

Factor	Total Numbers	Main drug categories				Musculo-skeletal System
		Cardiovascular system	Respiratory System	Central-nervous System	Endocrine System	
<b>Age (years)</b>						
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 years and over	715	608 (85)	135 (19)	513 (72)	101 (14)	59 (8)
<b>Gender</b>						
Women	6896	4813 (70)	1510 (22)	4528 (66)	1351 (20)	1260 (18)
Men	5979	4571 (76)	1351 (23)	2950 (49)	1565 (26)	883 (15)
<b>Deprivation**</b>						
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 sub-group

Table 3: Associations between individual study groups and higher multi-drug counts

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (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 (3.0-4.2)
<i>Prevalence ratio</i>	<i>0.2</i>	<i>0.4</i>	<i>0.5</i>	<i>1.5</i>	<i>2.3</i>	<i>3.3</i>	
CHD 'alone'	148	4057	4248	1372	160	16	1.0
CHD comorbidity	36	1027	3973	3516	1327	121	5.35 (4.6-6.3)
<i>Prevalence ratio</i>	<i>0.2</i>	<i>0.3</i>	<i>0.9</i>	<i>2.6</i>	<i>8.3</i>	<i>7.6</i>	
CVD 'alone'	688	4087	3848	1306	70	0	1.0
CVD comorbidity	41	1745	4251	3224	678	62	3.70 (2.8-5.0)
<i>Prevalence ratio</i>	<i>0.1</i>	<i>0.4</i>	<i>1.1</i>	<i>2.5</i>	<i>9.7</i>	<i>n/a</i>	
COPD 'alone'	940	2487	3496	2726	350	0	1.0
COPD comorbidity	189	946	2855	4117	1751	142	3.22 (2.6-4.0)
<i>Prevalence ratio</i>	<i>0.20</i>	<i>0.4</i>	<i>0.8</i>	<i>1.5</i>	<i>5.00</i>	<i>n/a</i>	
OA 'alone'	1378	2786	3722	1854	256	5	1.0
OA comorbidity	174	1260	3550	3420	1325	271	3.64 (3.1-4.3)
<i>Prevalence ratio</i>	<i>0.1</i>	<i>0.5</i>	<i>1.0</i>	<i>1.8</i>	<i>5.2</i>	<i>54</i>	
Depression 'alone'	1912	4140	3093	776	79	0	1.0
Depression comorbidity	325	1422	3555	3555	1082	62	7.11 (5.6-9.0)
<i>Prevalence ratio</i>	<i>0.17</i>	<i>0.34</i>	<i>1.15</i>	<i>4.58</i>	<i>13.7</i>	<i>n/a</i>	

\*Alone – people with disease alone and none of the other 5 morbidities, comorbidity is 1 or more of other 5 study morbidities, \*\*Comorbid drug 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 to 4 combined) compared to lower drug counts (2 or less), CHD is coronary heart disease and CVD is cerebro-vascular disease

**Table 4: Associations between vascular comorbidity groups and higher multi-drug counts**

Conditions	Multi-drug number/10,000 population						Adjusted Odds Ratio (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 (3.8-5.7)
<i>Prevalence ratio</i>	<i>0.43</i>	<i>0.29</i>	<i>0.71</i>	<i>1.65</i>	<i>2.60</i>	<i>1.90</i>	
Vascular group and OA	29	873	3493	3697	1557	349	3.01 (2.6-3.5)
<i>Prevalence ratio</i>	<i>0.15</i>	<i>0.37</i>	<i>0.87</i>	<i>1.45</i>	<i>2.01</i>	<i>3.92</i>	
Vascular group and Depression	69	829	3733	3917	1359	92	3.22 (2.6-3.9)
<i>Prevalence ratio</i>	<i>0.35</i>	<i>0.35</i>	<i>0.93</i>	<i>1.54</i>	<i>1.76</i>	<i>1.03</i>	

\*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 to 4 combined) compared to lower drug counts (2 or less)

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**Table 5: Key drug treatment of non-vascular conditions in vascular comorbidity**

Numbers (%)	Key drug treatments		Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (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 (0.43-0.78)	0.55 (0.40-0.75)
OA without vascular comorbidity	281 (16)	1440 (84)	1.0	1.0
OA and vascular comorbidity	117 (17)	568 (83)	0.95 (0.75-1.20)	0.82 (0.64-1.06)
Depression without vascular comorbidity	259 (16)	1378 (84)	1.0	1.0
Depression and vascular group	120 (28)	311 (72)	0.49 (0.38-0.62)	0.55 (0.42-0.73)

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

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
<b>Methods</b>			
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) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
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	5-7
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	n/a
<b>Results</b>			

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	8
		(b) Give reasons for non-participation at each stage	n/a
		(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	8
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers of outcome events or summary measures	8-9
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	8-9
		(b) Report category boundaries when continuous variables were categorized	n/a
		(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	n/a
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	9-10
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	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
<b>Other information</b>			
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	11

\*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](http://www.strobe-statement.org).