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Examining Patterns of Multimorbidity, Polypharmacy and Risk of Adverse Drug Reactions in Chronic Obstructive Pulmonary Disease: A Cross-Sectional UK Biobank Study

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3 1 **Examining Patterns of Multimorbidity, Polypharmacy and Risk of Adverse Drug Reactions in**

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5 2 **Chronic Obstructive Pulmonary Disease: A Cross-Sectional UK Biobank Study**

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44 20 **Word count: 3446**

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3 21 **Abstract**
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5
6 22 **Objective:** This study aims: (1) to describe the pattern and extent of multimorbidity and
7
8 23 polypharmacy in UK Biobank participants with chronic obstructive pulmonary disease (COPD); and
9
10 24 (2) to identify which comorbidities are associated with increased risk of adverse drug reactions
11
12 25 (ADRs) resulting from polypharmacy.
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14
15 26 **Design:** Cross-sectional analysis of UK Biobank.
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18 27 **Setting:** Community cohort.
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20
21 28 **Participants:** UK Biobank participants comparing self-reported COPD (n=8317) with no COPD
22
23 29 (n=494,323).
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25
26 30 **Outcomes:** Multimorbidity (\geq four conditions) and polypharmacy (\geq five medications) in participants
27
28 31 with COPD versus those without. Risk of ADRs (taking \geq three medications associated with falls,
29
30 32 constipation, urinary retention, central nervous system (CNS) depression, bleeding or renal injury) in
31
32 33 relation to the presence of COPD and individual comorbidities.
33

34
35 34 **Results:** Multimorbidity was more common in participants with COPD than those without (17% vs.
36
37 35 4%). Polypharmacy was highly prevalent (52% with COPD taking \geq five medications vs 18% in those
38
39 36 without COPD). Adjusting for age, sex and socioeconomic status, those with COPD were significantly
40
41 37 more likely than those without to be prescribed \geq 3 medications contributing to falls (Odds ratio (OR)
42
43 38 2.27, 95% confidence interval (CI) 2.13 to 2.42), constipation (OR 3.42, 95% CI 3.10 to 3.77), urinary
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45 39 retention (OR 3.38, 95% CI 2.94 to 3.87), CNS depression (OR: 3.75, 95% CI 3.31 to 4.25), bleeding
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47 40 (OR 4.61, 95% CI 3.35 to 6.19) and renal injury (OR 2.22, 95% CI 1.86 to 2.62). Comorbid
48
49 41 cardiovascular disease was associated with the greatest risk of taking \geq 3 medications associated with
50
51 42 falls/renal injury. Comorbid mental health conditions were most strongly associated with
52
53 43 medications linked with CNS depression/urinary retention/bleeding.
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55
56 44 **Conclusions:** Multimorbidity is common in COPD and associated with high levels of polypharmacy.
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58 45 Co-prescription of drugs with various ADRs is common. Medications contributing to this risk are
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60 46 largely indicated for the management of associated comorbidities rather than COPD. Future

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3 47 research should examine the effects on healthcare outcomes of co-prescribing multiple drugs with
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5 48 similar potential ADRs. COPD clinical guidelines should emphasise assessment of comorbidities and
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7 49 risk of ADRs.
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10 **Abstract word count: 325**
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19 **Strengths and Limitations**
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- 21 54 • This paper assesses multimorbidity, polypharmacy and risk of adverse drug reactions are
22
23 55 assessed in UK Biobank participants with self-reported COPD compared with those without
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25 56 COPD.
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27
28 57 • Baseline variables from the UK Biobank assessment centre were used to adjust for potential
29
30 58 confounders.
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32 59 • Cumulative risk of common adverse drug reactions was quantified by identifying UK Biobank
33
34 60 participants taking three or more medications associated with similar adverse drug
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36 61 reactions.
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38 62 • Analyses were repeated using a subgroup of participants with spirometry data confirming
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40 63 airflow obstruction.
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42 64 • Medication and comorbidity data rely on participant self-report, and may thus be
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44 65 susceptible to bias or inaccuracy.
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3 68 **BACKGROUND**
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6 69 In people with Chronic Obstructive Pulmonary Disease (COPD), multimorbidity (the presence of two
7
8 70 or more long-term conditions (LTCs)) is highly prevalent.(1-4) A recent meta-analysis of 29 datasets
9
10 71 demonstrated that those with COPD are significantly more likely to be diagnosed with a range of
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12 72 cardiovascular comorbidities than those without COPD (we will use the term comorbidity when
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14 73 referring to specific conditions in addition to COPD, and multimorbidity to refer to the presence of
15
16 74 two or more LTCs).(5) Other LTCs with known increased prevalence in COPD include obesity,(6)
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18 75 depression,(7-10) gastro-oesophageal reflux disease,(11-13) osteoporosis,(14-16) and lung
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20 76 cancer.(17, 18) Each of these comorbidities has been associated with poorer health related
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22 77 outcomes in COPD when compared to those with no comorbidity.(19-30) The overall burden of
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24 78 multimorbidity also impacts prognosis in COPD, for example higher number of comorbidities is
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26 79 associated with higher risk of mortality,(31) and higher burden of morbidity assessed using the
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29 80 Charlson index and the COPD-specific comorbidity test (COTE) is associated with higher risk of all-
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31 81 cause and respiratory specific mortality.(32, 33)
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37 83 Multimorbidity in the general population is associated with polypharmacy (often defined as
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39 84 concomitant use of ≥ 5 or ≥ 10 pharmacological agents).(34) Polypharmacy has been associated with
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41 85 increased risk of adverse drug reactions (ADRs)(35-37) and potentially preventable hospital
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43 86 admissions, particularly in the elderly.(38, 39) It has been demonstrated that diagnosis of COPD is
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45 87 associated with increased risk of polypharmacy.(40, 41) This is, in large measure, due to the high
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47 88 burden of extra-pulmonary comorbidities.(42) However, little is known about the risk of ADRs in the
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49 89 context of multimorbidity in COPD.
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3 91 Given the well-established burden of multimorbidity and polypharmacy in COPD, it is likely that
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5 92 those with COPD are at increased risk of ADRs resulting from polypharmacy. Previous analyses have
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7 93 not focused on the risk of specific ADRs, or assessed which comorbidities increase this risk, instead
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9 94 reporting overall counts of prescribed medication. Data collected for the UK Biobank cohort offers
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11 95 an opportunity to assess how multimorbidity in COPD relates to polypharmacy and to assess the
12
13 96 prevalence of co-prescription of medications with similar ADRs.
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19 98 This paper aims:

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22 99 • To describe the pattern and extent of multimorbidity and polypharmacy in UK Biobank
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24 100 participants with COPD.
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26 101 • To identify which comorbidities in people with COPD are associated with increased risk of
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28 102 ADRs resulting from polypharmacy.
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3 104 **METHODS**
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6 105 **Data collection**
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8 106 Between 2006 and 2010, UK Biobank recruited 502,640 participants aged 37 to 73. Participants
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10 107 underwent baseline assessments at one of 22 assessment centres throughout England, Scotland and
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12 108 Wales. Sociodemographic and lifestyle details were recorded using touchscreen questionnaires.
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14 109 Townsend scores were derived from participant postcodes to provide an area-based measure of
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16 110 socioeconomic deprivation. Self-reported LTCs, prescribed and over-the-counter medications,
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18 111 smoking status (current, previous or never) and frequency of alcohol intake (never / special
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20 112 occasions only, one-three times a month, at least once a week) were recorded from a touchscreen
21
22 113 questionnaire and subsequent verbal interview with a study nurse. Physical activity was self-
23
24 114 reported and classified into: none (no physical activity in the last four weeks), low (light 'DIY' activity
25
26 115 only in the last four weeks), medium (heavy DIY and/or walking for pleasure and/or other exercises
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28 116 in the last four weeks), high (strenuous sports in the last four weeks).
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30
31 117 Study centre staff also collected physical measures including height and weight (to calculate body
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33 118 mass index (BMI)) and spirometry. Spirometry was performed using a Vitalograph Pneumotrac 6800.
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35 119 Individual reasons for contraindications to attempting spirometry were not recorded but, according
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37 120 to protocol, these included chest infection in the last month, history of collapsed lung, and heart
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39 121 attack or surgery in the past three months. Full details of the Biobank spirometry protocol are
40
41 122 available at <https://biobank.ctsu.ox.ac.uk/crystal/docs/Spirometry.pdf>. In brief, participants were
42
43 123 allowed up to three attempts to provide two reproducible spirometry measurements. Where the
44
45 124 reproducibility of the first two was deemed acceptable (<5% variation in both FEV1 and FVC) a third
46
47 125 measurement was not performed. All values were recorded along with any error messages
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49 126 generated. As per the American Thoracic Society/European Respiratory Society (ATS/ERS) end-of-
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51 127 test criteria, we interpreted as valid any measurement with no error message or if 'user accepted'
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53 128 was specified.(43) No post-bronchodilator measurements were recorded, which deviates from the
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3 129 ATS/ERS guidelines and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines
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5 130 for COPD.(44, 45)

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8 131 Participants provided full informed consent to participate in UK Biobank and this study had full
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10 132 ethical approval from the NHS National Research Ethics Service for UK Biobank studies (Ref
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12 133 16/NW/0274).

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16 17 18 135 **Defining COPD**

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20 136 Participants reporting to have been diagnosed with chronic obstructive pulmonary disease, chronic
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22 137 bronchitis, or emphysema at the nurse-led interview were coded as having 'self-reported COPD'.

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24
25 138 Due to the potential inaccuracies of using self-reported diagnoses, we identified a subset of those
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27 139 with self-reported COPD who met an adaptation of the Global Initiative for Obstructive Lung Disease
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29 140 (GOLD) spirometry criteria for COPD.(45) This subset, referred to as 'GOLD COPD', was used as a
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31 141 sensitivity analysis for self-reported COPD, and to stratify findings by severity of airflow obstruction.

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33
34 142 For participants with self-report COPD and valid spirometry measurements, we calculated the ratio
35
36 143 of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) using the highest

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38 144 measurement for each participant meeting the American Thoracic Society/European Respiratory
39
40 145 Society end-of-test criteria.(43) Those with a FEV1/FVC ratio <0.7 were classed as having an

41
42 146 obstructive deficit and thus meeting the GOLD diagnostic criteria for COPD. We used the Hankinson
43
44 147 equation,(46) based on recorded age, sex and height, to calculate predicted FEV1 values for each

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46 148 participant. Those with GOLD COPD were classified on the basis of their best available FEV1
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48 149 measurement as having mild (>80% predicted FEV1), moderate (50-80% predicted FEV1), or severe
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50 150 (<50% predicted FEV1) airflow obstruction in line with the GOLD COPD guidelines.(45)

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3 152 **Defining comorbidities and medications**
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6 153 All morbidities were defined by self-report. For the purposes of examining the number of
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8 154 comorbidities reported, a count (1,2,3,4 or ≥ 5) was taken from a list of 42 morbidities originally
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10 155 established for a large epidemiological study in Scotland, through systematic review, the Quality and
11
12 156 Outcomes Framework, NHS Scotland and an expert panel (47), and subsequently amended for UK
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14 157 Biobank (48). Morbidities were categorised for the purposes of this analysis into cardiovascular
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16 158 disease, gastrointestinal disease, mental health conditions, cancer, and painful conditions. Full
17
18 159 details of conditions comprising each category can be found in appendix 1.

20
21 160 Medication data were collected by self-report. Medications were coded by mechanism of action
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23 161 according to the British National Formulary (BNF) (e.g. Angiotensin-converting enzyme inhibitors,
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25 162 beta-blockers, calcium channel blockers, etc.). For some situations where more than one medication
26
27 163 with a similar mechanism of action may be commonly co-prescribed (e.g. aspirin and clopidogrel,
28
29 164 both antiplatelets) these were coded separately. A complete list of the medications coded within
30
31 165 each class can be found in appendix 2.

33
34 166 We defined those at risk of specific ADRs as anyone on 3 or more medications with similar potential
35
36 167 ADRs, based on information provided in the *Scottish Government Model of Care Polypharmacy*
37
38 168 *Working Group: Polypharmacy Guidance*.(49) This guideline cross-tabulates commonly prescribed
39
40 169 medications with common ADRs to help identify those at cumulative risk of ADRs. This document
41
42 170 groups common medications by similar potential ADRs. While this list is not all-inclusive, and the cut-
43
44 171 off value of three or more medications is arbitrary, this does allow an estimation of the cumulative
45
46 172 risk of specific ADRs. We identified six potential ADRs (falls/fractures, constipation, urinary
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48 173 retention, CNS depression, bleeding and renal injury) for which the proportion of participants taking
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50 174 three or more associated medications could be assessed.

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3 176 **Statistical analysis**
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6 177 Study hypothesis was made an analyses planned prior to inspection of the data.
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9 178 Baseline variables

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11 179 Comparisons were made between participants with self-reported COPD and the rest of the cohort
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13 180 (who did not report COPD). Age, sex, smoking status, deprivation (Townsend score), BMI, physical
14
15 181 activity and frequency of alcohol intake were compared using χ^2 test for categorical variables, χ^2 test
16
17 182 for trend for ordinal variables, and Mann-Whitney-U test for continuous variables. Total number of
18
19 183 morbidities, prevalence of specific morbidities, number of self-reported prescribed medications, and
20
21 184 proportion of participants taking each class of medication (Appendix 2), were also compared
22
23 185 between those with self-reported COPD and the rest of the cohort. All comparisons were repeated
24
25 186 comparing participants with GOLD COPD only with those without COPD, stratifying by severity of
26
27 187 airflow obstruction.
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31 188 **Multimorbidity and polypharmacy**
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34 189 Logistic regression analyses were used to compare participants with self-reported COPD and those
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36 190 without COPD. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for:

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39 191 • the presence of cardiovascular disease, cancer, gastrointestinal disease, mental health
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41 192 conditions and painful conditions
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43 193 • the presence of four or more morbidities (excluding COPD)
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45 194 • the use of five or more, and 10 or more, medications (two separate models)
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48 195 Models were initially adjusted for age, sex and socioeconomic deprivation (model 1), then adjusted
49
50 196 for the addition of smoking status, alcohol frequency, BMI and physical activity (model 2). These
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52 197 analyses were repeated comparing those with GOLD COPD only to those without COPD.
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55 198 **Risk of ADRs**
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3 199 For each potential ADR (falls/fractures, constipation, urinary retention, CNS depression, bleeding
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5 200 and renal injury) participants taking three or more medications associated with that ADR were
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7 201 identified. The following comparisons were then made:

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10 202 • Unadjusted percentages at risk of each ADR were calculated for participants without COPD,
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12 203 with self-reported COPD, and with self-reported COPD plus each category of comorbidity
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14 204 (cardiovascular disease, cancer, gastrointestinal disease, mental health conditions and
15
16 205 painful conditions) to give an impression of the ADR risk in COPD, and identify comorbidities
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18 206 that may increase this risk.
- 19
20 207 • ORs of being at risk of each ADR were calculated comparing those with self-reported COPD
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22 208 to those without COPD adjusting for age, sex and socioeconomic deprivation (model 1) and
23
24 209 for age, sex, socioeconomic deprivation, smoking status, alcohol frequency, BMI and physical
25
26 210 activity (model 2).
- 27
28 211 • ORs of being at risk of each ADR were calculated comparing those with and without self-
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30 212 reported COPD in each comorbidity category to (i.e. participants with cardiovascular disease
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32 213 alone compared to participants with cardiovascular disease plus COPD, etc.). This was
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34 214 intended to identify whether specific patterns of multimorbidity in COPD are associated with
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36 215 increased ADR risk. Adjustment for a wide range of potential confounders was not
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38 216 appropriate in these models due to the smaller number of participants in each model.

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42 217 Each analysis was repeated comparing GOLD COPD only to those without COPD. Less than 3% of
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44 218 participants (with or without COPD) had missing data for potential confounding variables (table 1).
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46 219 Those with missing data were excluded from adjusted analyses. Spirometry data were missing for
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48 220 3591 participants with self-report COPD (43%), hence the use of the GOLD COPD subset as a
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50 221 sensitivity analysis.

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53 222 All analyses were performed using R statistical software (version 3.3.1).
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6 224 **RESULTS**
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8 225 At the time of recruitment, 8317 participants reported having COPD (1.7%) and are referred to here
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10 226 as the self-report COPD group. Of those who self-reported COPD, 4726 (57%) had valid spirometry
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12 227 measurements. Spirometry was contraindicated or not available in 2507 of those with self-reported
13
14 228 COPD. Spirometry measurements did not meet the ATS/ESR end-of-test criteria in 1084
15
16 229 participants.(43) Of those with valid spirometry, 2620 (55%) met the GOLD criteria for airflow
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18 230 obstruction (399 (15%) mild, 1409 (54%) moderate, 812 (31%) severe, see Figure 1) and are referred
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20
21 231 to here as GOLD COPD.
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27 233 **Baseline variables**
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29
30 234 Table 1 describes and compares the characteristics of those with and without COPD in UK Biobank.
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32 235 Participants with COPD (both self-report and GOLD) were significantly older, more socioeconomically
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34 236 deprived, and less physically active. A higher proportion of those with COPD were male, obese and
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36 237 had a history of smoking.
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Table 1. Baseline variables								
Characteristic	No COPD n=494323		COPD (self-report) n=8317			GOLD GOPD n=2620		
	Count	%	Count	%	p-value	Count	%	p-value
Sex								
Male	224906	45.5	4268	51.3		1426	54.4	
Female	269417	54.5	4049	48.7	<0.001	1194	45.6	<0.001
Age	Median: 58 IQR: 50-63		Median: 62 IQR: 57-66		<0.001	Median: 63 IQR: 59-66		<0.001
Ethnicity								
White	464770	94.5	8052	97.3		2620	100	
Other	26821	5.4	219	2.6	<0.001	0	0	<0.001
Missing	2732		46			0	0	
Socioeconomic deprivation quintile								
1 (least deprived)	99672	20.2	1015	12.2		309	11.8	
2	98977	20.0	1142	13.7		362	13.8	
3	99013	20.1	1399	16.8		440	16.8	
4	98660	20.0	1735	20.9		580	22.2	
5 (most deprived)	98385	19.7	3015	36.3	<0.001	926	35.4	<0.001
Missing	616		11			3		
Smoking status								
Current	50817	10.3	2172	26.3		833	32.2	
Previous	169015	34.4	4083	49.5		1398	54.0	
Never	271602	55.3	1999	24.2	<0.001	360	13.9	<0.001
Missing	2889		63			29		
Alcohol frequency								
Daily	100070	20.3	1720	20.7		618	23.6	
3-4 times/week	114058	23.1	1404	16.9		475	18.2	
1-2 times/week	127459	25.9	1863	22.5		561	21.5	
1-3 times/month	54979	11.2	894	10.8		289	11.1	
Occasional	56707	11.5	1322	15.9		387	14.8	
Never	39569	8.0	1092	13.2	<0.001	284	10.9	<0.001
Missing	1481		22			6		
BMI								
<18.5	2478	0.5	148	1.8		56	2.2	
18.5-24.9	155282	31.8	2185	26.8		829	31.9	
25.0-29.9	211102	43.2	3165	38.9		1049	40.4	
>30	119813	24.5	2647	32.5	<0.001	665	25.6	<0.001
Missing	5648		172			21		
Physical activity								
High	49827	10.6	250	3.1		70	2.7	
Medium	387766	79.6	5838	72.0		1902	73.3	
Low	18354	3.8	589	7.3		203	7.8	
None	31425	6.4	1433	17.7	<0.001	421	16.2	<0.001
Missing	6951		207			24		
FEV1 (% predicted)								
>80	272109	78.0	1853	39.2		399	15.2	
50-79	71727	20.6	2022	42.8		1409	53.8	
<50	4841	1.4	851	18.0	<0.001	812	31.0	<0.001
Missing	145646		3591			1061		

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3 240 **Multimorbidity and polypharmacy**
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6 241 Prevalence of each category of comorbidity was higher in those with COPD than without (table 2).
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8 242 After controlling for age, sex and socioeconomic status, those with self-reported COPD were
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10 243 significantly more likely than those without to have each category of comorbidity examined:
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12 244 cardiovascular disease (OR 1.45; 95% confidence interval (CI) 1.39 to 1.52) , cancer (1.29; 1.2 to
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14 245 1.39), gastrointestinal disease (1.76; 1.67 to 1.86) , mental health conditions (2.02; 1.89 to 2.15) ,
15
16 246 and painful conditions (1.54; 1.46 to 1.62). Results for GOLD COPD also suggested higher likelihood
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18 247 of each comorbidity compared to those without COPD, although the ORs were lower and results for
19
20 248 cancer not statistically significant (appendix 3). Results were similar after adjusting for additional
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22 249 confounders (smoking status, alcohol frequency, BMI and physical activity) with the exception of
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24 250 cardiovascular comorbidity in GOLD COPD, which was no longer significantly associated (1.08; 0.99
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26 251 to 1.18) (appendix 3).
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Table 2: Comorbidities in those with and without COPD						
	Control n=494323 count (%)	Self-report COPD n=8317 count (%)	GOLD COPD			
			All n=2620 count (%)	Mild n=399 count (%)	Moderate n=1409 count (%)	Severe n= 812 count (%)
Total comorbidities (excluding COPD) ≥ 4	19959 (4.0)	1389 (16.7)**	331 (12.6)**	46 (11.5)	191 (13.5)	94 (11.6)
Total number of medications ≥ 1	356406 (72.1)	7670 (92.2)**	2452 (93.6)**	352 (88.2)	1321 (93.8)	779 (95.9)
≥ 5	87286 (17.7)	4312 (51.8)**	1349 (51.5)**	171 (42.9)	702 (49.8)	476 (58.6)
≥ 10	10678 (2.2)	1269 (15.3)**	329 (12.6)**	31 (7.8)	172 (12.2)	126 (15.5)
Prevalence of comorbidities						
Cardiovascular	152891 (30.9)	3957 (47.6)**	1156 (44.1)**	142 (35.6)	611 (43.4)	403 (49.6)
Hypertension	130119 (26.3)	3206 (38.5)**	916 (35.0)**	112 (28.1)	483 (34.3)	321 (39.5)
CHD	21560 (4.4)	1171 (14.1)**	315 (12.0)**	31 (7.6)	185 (13.1)	99 (12.2)
Diabetes	24737 (5.0)	766 (9.1)**	189 (7.2)**	16 (4.0)	109 (7.7)	64 (7.9)
Stroke/TIA	8459 (1.7)	395 (4.7)**	98 (3.7)**	11 (2.8)	51 (3.6)	36 (4.4)
AF	3552 (0.7)	99 (1.2)**	34 (1.3)**	3 (0.8)	16 (1.1)	15 (1.8)
Heart failure	768 (0.2)	35 (0.4)**	6 (0.2)	0	1 (0.1)	5 (0.6)
Respiratory						
Asthma	55245 (11.2)	3048 (36.6)**	984 (37.6)**	142 (35)	523 (37.1)	319 (39.3)
PE/DVT	12316 (2.5)	554 (6.7)**	139 (5.3)**	29 (7.3)	71 (5.0)	39 (4.8)
Bronchiectasis	968 (0.2)	167 (2.0)**	39 (1.5)**	7 (1.8)	17 (1.2)	15 (1.8)
Pulmonary fib.	504 (0.1)	67 (0.8)**	18 (0.7)**	3 (0.8)	12 (0.9)	3 (0.4)
Cancer	37686 (7.6)	937 (11.3)	272 (10.4)	47 (11.8)	146 (10.4)	79 (9.7)
Lung	405 (0.1)	52 (0.6)**	15 (0.6)**	0	7 (0.5)	8 (1.0)
Breast	11311 (2.3)	210 (2.5)*	57 (2.2)	12 (3.0)	30 (2.1)	15 (1.8)
Prostate	3588 (0.7)	105 (1.3)**	30 (1.1)*	5 (1.3)	12 (0.9)	13 (1.6)
GI	2925 (0.6)	96 (1.2)**	34 (1.3)**	6 (1.5)	19 (1.3)	9 (1.1)
Haem	6170 (1.2)	124 (1.5)*	34 (1.3)	5 (1.3)	17 (1.2)	12 (1.5)
Gastrointestinal	55635 (11.5)	1737 (20.9)**	468 (17.9)**	76 (19.0)	254 (18.0)	138 (17.0)
Dyspepsia	37819 (7.7)	1257 (15.1)**	348 (13.3)**	53 (13.3)	189 (13.4)	106 (13.1)
Diverticular dis	5181 (1.0)	224 (2.7)**	54 (2.1)**	6 (1.5)	32 (2.3)	16 (2.0)
IBS	11203 (2.3)	291 (3.5)**	64 (2.4)**	17 (4.3)	35 (2.5)	12 (1.5)
CLD	935 (0.2)	36 (0.4)**	10 (0.4)*	2 (0.5)	10 (0.7)	3 (0.4)
Mental Health	35822 (7.2)	1127 (13.6)**	304 (11.6)**	54 (13.5)	162 (11.5)	88 (10.8)
Depression	27578 (5.6)	901 (10.8)**	233 (8.9)**	42 (10.5)	128 (9.1)	63 (7.8)
Anxiety	8781 (1.8)	245 (2.9)**	69 (2.6)**	13 (3.3)	36 (2.6)	20 (2.5)
Schizophrenia/ bipolar	1918 (0.4)	79 (0.9)**	27 (1.0)**	3 (0.7)	15 (1.1)	9 (1.1)
Other						
Painful condition	81733 (16.5)	2259 (27.2)**	655 (25.0)**	115 (28.8)	367 (26.0)	173 (21.3)
Osteoporosis	7700 (1.6)	342 (4.1)**	128 (4.9)**	21 (5.3)	67 (4.8)	40 (4.9)
Connective tissue disease	10642 (2.2)	391 (4.7)**	112 (4.3)**	19 (4.8)	72 (5.1)	21 (2.6)

Compared with control (χ^2): * : p<0.05, ** : p<0.001

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3 255 Morbidity counts (excluding COPD) and counts of prescribed medication are shown in table 2
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5 256 comparing those with COPD, stratified by severity of airflow obstruction, with those without. Those
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7 257 with COPD had higher numbers of LTCs and more prescribed medications than those without. There
8
9 258 was a trend towards more prescribed medications in those with greater severity of airway
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11 259 obstruction. After controlling for age, sex and socioeconomic status, those with self- report COPD
12
13 260 were more likely to report ≥ 4 comorbidities (3.49; 3.28 to 3.71), ≥ 5 medications (3.85; 3.68 to 4.03),
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15 261 and ≥ 10 medications (5.72; 5.36 to 6.10) than those without COPD. Results were similar for GOLD
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17 262 COPD and remained statistically significant after adjusting for smoking status, alcohol frequency,
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19 263 BMI and physical activity (appendix 3).

22 264 **ADR Risk**

25 265 Counts and percentages of participants taking specific medications are shown in appendix 4.
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27 266 Participants with COPD (self-report and GOLD) were more likely than those without COPD to be
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29 267 prescribed drugs across a range of disease areas, reflecting the range of comorbidities present
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31 268 among those with COPD. The percentages of participants within each category (no COPD, COPD, and
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33 269 COPD with specific comorbidities) taking three or more medications associated with a similar ADR is
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35 270 shown in Figure 2. For each category of ADR a higher proportion of participants with COPD reported
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37 271 taking three or more associated medications than those without COPD. This increased further with
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39 272 comorbidities, with COPD plus cardiovascular comorbidity associated with the highest percentage
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41 273 taking multiple medications with a risk of falls or renal injury, and those with COPD plus mental
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43 274 health conditions showing the highest percentages taking multiple medications with a risk of
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45 275 constipation, CNS depression or bleeding.

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52 277 After adjusting for age, sex and socioeconomic deprivation, those with self-report COPD remained
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54 278 more likely to be taking three or more medications in each category than those without COPD. These

findings remained statistically significant after adjusting for smoking status, alcohol frequency, BMI and physical activity (Table 3). Findings were similar for GOLD COPD however, after adjusting for additional potentially confounding variables, results for bleeding risk were not statistically significant in this sensitivity analysis (Table 3).

Table 3. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs

ADR	Self-report COPD compared with no COPD N=502,640		GOLD COPD compared with no COPD N=496,943	
	Model 1 N=502,013	Model 2 N=487,718	Model 1 N=496,943	Model 2 N=482,378
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Falls	2.27 (2.13 – 2.42) ***	1.83 (1.71-1.96) ***	1.66 (1.47 – 1.87) ***	1.49 (1.30-1.69) ***
Constipation	2.71 (2.54 – 2.89) ***	2.66 (2.39-2.96) ***	2.18 (1.77 – 2.64) ***	1.82 (1.47-2.24) ***
Urinary retention	3.38 (2.94 – 3.87) ***	2.59 (2.22-3.0) ***	1.98 (1.44 – 2.64) ***	1.64 (1.18-2.21) **
CNS depression	3.75 (3.31 – 4.25) ***	2.81 (2.45-3.22) ***	2.29 (1.73 – 2.95) ***	1.87 (1.40-2.43) ***
Bleeding	4.60 (3.35 – 6.19) ***	3.39 (2.40-4.66) ***	2.63 (1.25 – 4.80) **	1.76 (0.75-3.48) §
Renal injury	2.22 (1.86 – 2.62) ***	1.84 (1.53-2.19) ***	1.94 (1.41 – 2.58) ***	1.84 (1.33-2.49) ***

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
 Model 1: Adjusted for age, sex and socioeconomic status
 Model 2: Adjusted for age, sex, socioeconomic status, smoking, alcohol frequency, body mass index and physical activity

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Finally, each category of ADR risk was assessed in a subgroup analysis for each category of comorbidity (cardiovascular, GI, cancer, mental health and painful conditions) comparing those with and without COPD (e.g. participants with cardiovascular disease plus COPD compared with participants with cardiovascular disease alone, etc.). These models were adjusted for age, sex and socioeconomic status only. Within each category of comorbidity, those with self-reported COPD were more likely to be at risk of each ADR than those without COPD (appendix 3). Not all results were statistically significant when using GOLD COPD (Appendix 3).

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3 296 **DISCUSSION**

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6 297 **Summary of main findings**

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8 298 Multimorbidity and polypharmacy in COPD were common among UK Biobank participants. The
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10 299 presence of one or more comorbidity was highly prevalent in those with COPD (85%). More than half
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12 300 reported polypharmacy (five or more medications), and 15% reported 10 or more medications. The
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14 301 prevalence of cardiovascular disease, as well as the degree of polypharmacy, was higher among
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16 302 those with more severe airflow obstruction.
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20 303 For the first time, our data demonstrates that those with COPD were more likely than those without
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22 304 to be prescribed multiple medications (\geq three) with similar ADRs. Those with COPD plus
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24 305 cardiovascular comorbidity were most likely to be taking multiple medications with a risk of falls and
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26 306 of renal injury, while those with COPD plus comorbid mental health conditions were most likely to
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28 307 be taking medications causing constipation, CNS depression and bleeding. Within each category of
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30 308 comorbidity, those with COPD were more likely to be taking multiple medications with similar ADRs
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32 309 than those without. These associations between patterns of multimorbidity and specific ADR risks
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34 310 have not been described or quantified previously.
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40 312 **Strengths and limitations**

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43 313 Strengths of this study include the large sample size with representation from different areas of the
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45 314 UK. The range of data collected at UK Biobank assessment centres meant it was possible to compare
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47 315 a range of sociodemographic characteristics as well as spirometry data, the latter being unusual for a
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49 316 large community based cohort. It is recognised, however, that UK Biobank participants show some
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51 317 evidence of 'healthy volunteer bias', differing from the UK average on a number of socioeconomic,
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53 318 lifestyle and health-related measures. Specifically they are less socioeconomically deprived, less
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55 319 likely to smoke, to be obese, and have fewer self-reported health conditions.(50) All LTC diagnoses
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3 320 as well as medication data were self-reported, with no alternative means of verification. We
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5 321 attempted to minimise this limitation by identifying a subset of those with COPD meeting the GOLD
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7 322 diagnostic criteria and repeating the analyses with this subset. Importantly, spirometry values were
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9 323 also pre-bronchodilator, which is in contravention to guidelines for diagnosing COPD. Additionally,
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11 324 information was not available about the strength of indication for medications and individual
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13 325 susceptibility to risk, which is a limitation when considering the risk of ADRs.

16 326 The use of the Scottish Government Polypharmacy Guideline allowed analysis of potential ADR risk
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18 327 by specific common ADRs. The intended purpose of this guideline, however, was not to identify
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20 328 potential risk from a population sample, but rather to identify potential causes of symptoms or
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22 329 complications. The analysis in this study, therefore, serves only as an approximation of potential risk,
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24 330 not an absolute marker of inappropriate polypharmacy. The cross-sectional nature of this analysis
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26 331 also precludes an analysis of actual harm as a result of polypharmacy. Despite these limitations,
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28 332 however, the co-prescription of multiple medications with similar ADRs strongly implies greater
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30 333 potential for harm. The association of such prescribing patterns with COPD, across a range of
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32 334 potential ADRs, is clear from our findings. This analysis is, to the author's knowledge, the first to
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34 335 attempt to quantify this risk for specific ADRs in this way.
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41 337 **Context and implications**

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44 338 The increased prevalence of individual comorbid conditions such as coronary heart disease,
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46 339 hypertension, diabetes, dyspepsia, osteoporosis, cancer, depression and anxiety in those with COPD
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48 340 is similar to the findings from other population based studies of comorbidities in COPD.(5, 11, 51-53)
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50 341 Our finding that cardiovascular disease prevalence increased with increasing severity of COPD is in
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52 342 keeping with the body of literature on cardiovascular comorbidities and COPD, in which high
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54 343 prevalence has been observed in (usually older) cohorts with severe airflow limitation.(5, 21)
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3 344 Greater polypharmacy with greater severity of COPD has also been observed previously in older
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5 345 COPD populations,(41, 54) although such analyses have been smaller (n=1859 and 398, respectively)
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7 346 and have not assessed the specific patterns of prescribing in COPD. To the best of our knowledge, no
8
9 347 previous studies have assessed the risk of ADRs as a result of polypharmacy in COPD. A recent
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11 348 population-based analysis of prescribing data from 310,000 adults in Scotland showed that over 15
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13 349 years from 1995 to 2010 the proportion of people with polypharmacy and with potentially serious
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15 350 drug-to-drug interactions increased dramatically.(35) The number of prescribed medications was
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17 351 also associated with increased risk of interactions. Our analysis differs in approach from this analysis,
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19 352 by seeking to identify patterns of prescribing increasing risk of specific adverse events, rather than
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21 353 counting total potential interactions. The strength of our approach lies in highlighting specific
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23 354 patterns of comorbidity in which specific ADRs are more likely. Our findings can therefore be applied
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25 355 to clinical practice, highlighting the importance of recognising comorbidity in COPD and being alert
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27 356 to specific ADRs when prescribing medication.
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34 358 Our findings indicate that in those with COPD the potential for ADRs as a result of combinations of
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36 359 medications is high, and this appears to be the result of a high prevalence of extra-pulmonary
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38 360 comorbidities. Clinical guidelines for COPD should place greater emphasis on the need for
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40 361 assessment of associated comorbidities and the risk of associated ADRs. While our analysis shows
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42 362 potential areas where ADR risk exists in COPD (e.g. falls with comorbid cardiovascular disease, CNS
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44 363 depression, constipation with comorbid mental health conditions), future research is merited to
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46 364 assess what actual harm could be attributed to such prescribing patterns.
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365 **Conclusion**

366 Among UK Biobank participants with COPD there was considerable multimorbidity and
367 polypharmacy. Those with COPD were highly likely to be concurrently prescribed multiple

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3 368 medications with similar potential adverse effects. Medications contributing to this risk were
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5 369 largely indicated for the management of the associated comorbidities rather than COPD. Future
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7 370 research should examine the effects on healthcare outcomes of co-prescribing of multiple drugs
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9 371 with similar potential of ADRs. Clinical guidelines for COPD should emphasise the need for
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11 372 assessment of comorbidities and the risk of associated ADRs.
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16 17 374 **Ethics approval and consent to participate**

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20 375 Participants provided full informed consent to participate in UK Biobank and this study was covered
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22 376 by the generic ethical approval for UK Biobank studies from the NHS National Research Ethics
23
24 377 Service (Ref 16/NW/0274).
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29 30 379 **Availability of data and materials**

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33 380 UK Biobank data is available via www.ukbiobank.ac.uk. Syntax for the generation of derived
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35 381 variables and for the analysis used for this study will be submitted to UK Biobank for record.
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40 41 383 **Competing interests**

42
43 384 The authors declare that they have no competing interests
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46 385

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3 389 **Author contributions**
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6 390 All authors (PH, BN, BJ, RM, DL, KG and FM) were involved in the conceptualisation and design of the
7
8 391 project and interpretation of results. PH carried out the analysis with support from BJ, RM and BN.
9
10 392 DL provided statistical support. All authors had access to the data. PH wrote the first draft of the
11
12 393 paper and all authors commented on subsequent drafts. All authors approved the final draft for
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14 394 publication. FM is guarantor.
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31 400 **References**

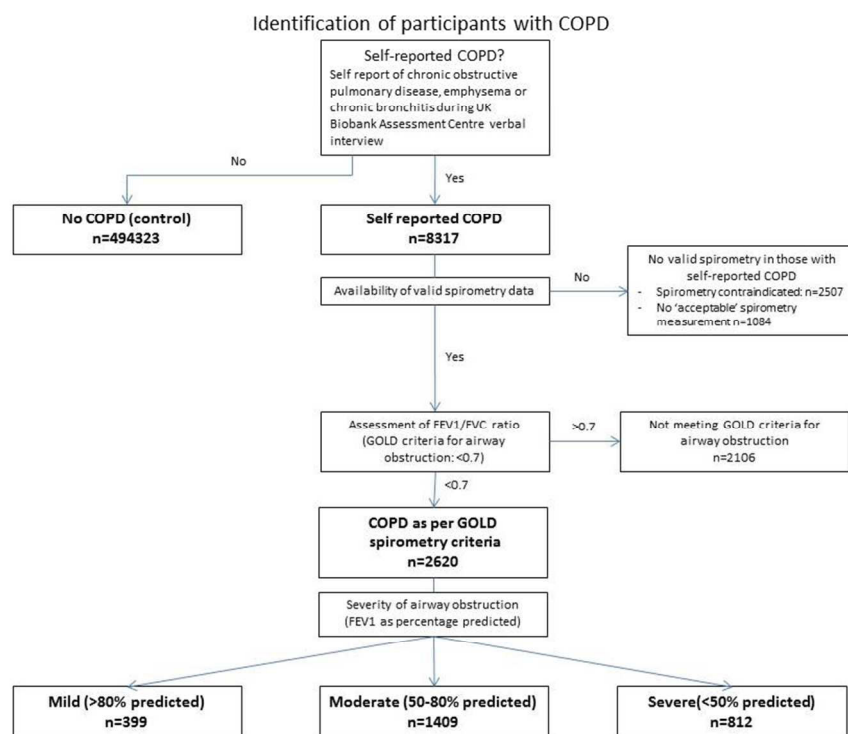
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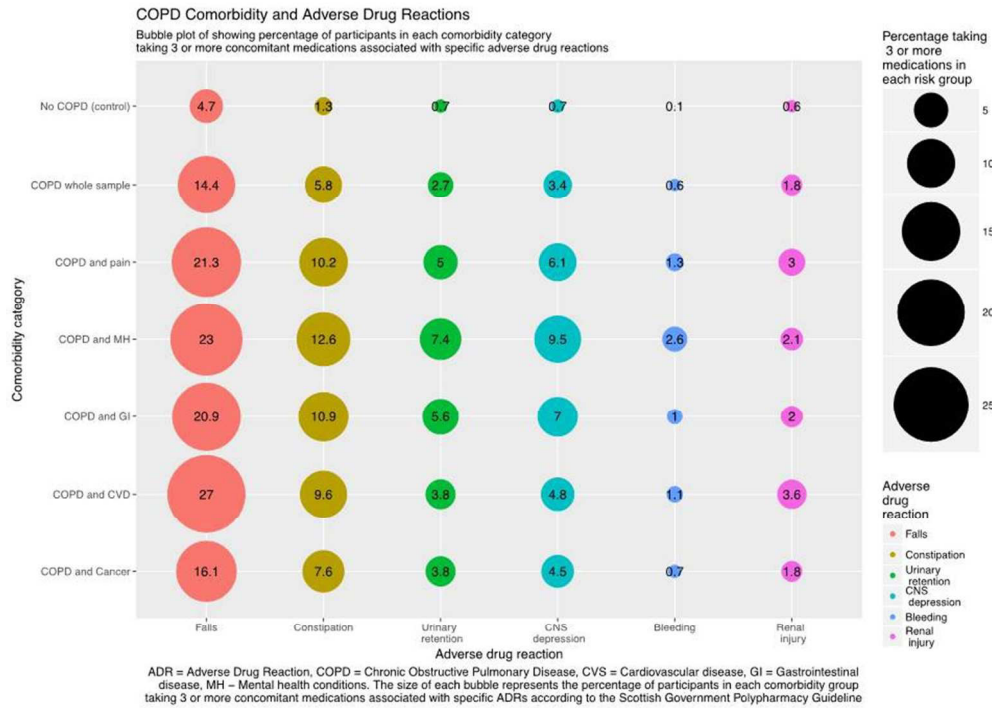
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Identification of participants with self-report COPD and GOLD COPD

254x190mm (96 x 96 DPI)



Bubble plot showing percentage of participants in each comorbidity category taking 3 or more concomitant medications associated with specific adverse drug reactions.

254x190mm (96 x 96 DPI)

Comorbidity category (used in analysis)	Conditions included (as reported in table 2)	Self-reported conditions comprising this condition (UK Biobank variables used to identify self-reported conditions)
Cardiovascular conditions	Hypertension	Hypertension Essential hypertension
	Coronary heart disease	Heart attack/MI Angina
	Diabetes	Diabetic nephropathy Diabetic neuropathy/ulcers Diabetes Type 1 diabetes Type 2 diabetes Diabetic eye disease
	Stroke/TIA	Stroke TIA Subarachnoid haemorrhage Brain haemorrhage Ischaemic stroke
	Atrial fibrillation	Atrial fibrillation
	Heart failure	Cardiomyopathy Hypertrophic cardiomyopathy Heart failure/pulmonary oedema
	Peripheral vascular disease	Peripheral vascular disease Leg claudication/intermittent claudication
Respiratory	COPD	COPD/Chronic obstructive pulmonary disease Emphysema/Chronic bronchitis Emphysema
	Asthma	Asthma
	PE/DVT	Deep vein thrombosis Pulmonary embolism
	Bronchiectasis	Bronchiectasis
	Pulmonary fibrosis	Pulmonary fibrosis
Cancer	Cancer	"yes"/"no" to "have you ever had cancer?"
Gastrointestinal	Dyspepsia	Gastro-oesophageal reflux (GORD) Oesophagitis/Barrett's oesophagus Gastric stomach ulcers Gastric erosions/gastritis Duodenal ulcer Dyspepsia/indigestion Hiatus hernia Helicobacter pylori
	Diverticular disease	Diverticular disease/diverticulitis

	Irritable bowel syndrome	Irritable bowel syndrome
	Chronic liver disease	Oesophageal varices Non infective hepatitis Liver failure/cirrhosis Primary biliary cirrhosis
	Inflammatory bowel disease	Inflammatory bowel disease Crohn's disease Ulcerative colitis
	Constipation	Constipation
	Viral hepatitis	Hepatitis B Hepatitis C Hepatitis D
Mental Health	Depression	Depression Postnatal depression
	Anxiety	Anxiety/panic attacks Nervous breakdown Post-traumatic stress disorder Obsessive compulsive disorder Stress Insomnia Psychological/psychiatric problem
	Schizophrenia	Schizophrenia
	Bipolar	Mania Bipolar disorder Manic depression
Painful conditions	Painful conditions	Back pain Joint pain Headaches (not migraine) Sciatica Plantar fasciitis Carpal tunnel syndrome Fibromyalgia Arthritis Shingles Disc problem Prolapsed disc/slipped disc Spine arthritis/spondylitis Ankylosing spondylitis Back problem Osteoarthritis Gout Cervical spondylosis Trigeminal neuralgia Disc degeneration Trapped nerve/compressed nerve
Other	Osteoporosis	Osteoporosis
	Connective tissue disease	Myositis/myopathy Systemic lupus erythematosus/SLE

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		Connective tissue disorder Sjogren's syndrome sicca syndrome Dermatopolymyositis Scleroderma/systemic sclerosis Rheumatoid arthritis Psoriatic arthropathy Dermatomyositis Polymyositis Polymyalgia rheumatica
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For peer review only

Drugs with cumulative risk of Adverse Drug Reactions*	
Adverse Drug Reaction	Contributing drug classes (participants taking 3 or more considered 'at risk' for the purposes of analysis)
Falls	H2-receptor blockers Loperamide Prochlorperazine Metoclopramide ACE-inhibitor/Angiotensin receptor blocker Thiazide diuretic Loop diuretic Amiloride/triamterene Spironolactone Beta-blocker Calcium-channel blocker Nitrates or nicorandil Digoxin Oral steroids Opiates Benzodiazepines Sedative antihistamines H1-receptor blockers Antipsychotics Tricyclic antidepressants Sulfonylureas/gliptins/glinides Pioglitazone Urinary antispasmodics Dosulepin Alpha-blockers
Constipation	H2-receptor blockers Laxatives Loperamide Prochlorperazine Thiazide diuretics Loop diuretics Calcium-channel blockers Opiates Sedative antihistamines H1-receptor blockers Antipsychotics Tricyclic antidepressants Urinary antispasmodics Dosulepin
Urinary retention	H2-receptor blockers Loperamide Prochlorperazine Opiates Sedative antihistamines H1-receptor blockers Antipsychotics Tricyclic antidepressants

	Urinary antispasmodics Dosulepin
CNS depression	H2-receptor blockers Loperamide Prochlorperazine Oral steroids Opiates Benzodiazepines Sedative antihistamines H1-receptor blockers Antipsychotics Tricyclic antidepressants Urinary antispasmodics Dosulepin
Bleeding	Aspirin Clopidogrel Other antiplatelets Oral steroids SSRIs and related drugs Non-steroidal anti-inflammatory drugs Warfarin
Renal injury	ACE-inhibitor/angiotensin receptor blockers Thiazide diuretic Loop diuretic Amiloride/triamterene Spironolactone Antibiotics/antifungals Non-steroidal anti-inflammatory drugs
Adapted from <i>Scottish Government Model of Care Polypharmacy Working Group. Polypharmacy Guidance (2nd edition) March 2015. Scottish Government.</i>	

Table S1. Odds ratios (with 95% CI) for the presence of categories of comorbidity

Comorbidity category	Self-report COPD compared with no COPD N=502,640		GOLD COPD compared with no COPD N=496,943	
	Model 1 N=502,013	Model 2 N=487,718	Model 1 N=496,324	Model 2 N=482,378
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Cardiovascular disease	1.45 (1.39-1.52) ***	1.28 (1.22-1.34) ***	1.11 (1.02-1.20) *	1.08 (0.99-1.18) §
Cancer	1.29 (1.20-1.39) ***	1.22 (1.13-1.31) ***	1.12 (0.99-1.27) §	1.06 (0.92-1.19) §
Gastrointestinal disease	1.76 (1.67-1.86) ***	1.56 (1.48-1.65) ***	1.4 (1.26-1.54) ***	1.24 (1.12-1.38) ***
Mental health	2.02 (1.89-2.15) ***	1.62 (1.51-1.73) ***	1.75 (1.54-1.97) ***	1.40 (1.22-1.58) ***
Painful conditions	1.54 (1.46-1.62) ***	1.35 (1.28-1.42) ***	1.31 (1.19-1.43) ***	1.16 (1.06-1.28) **

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
 Model 1: Adjusted for age, sex and socioeconomic status
 Model 2: Adjusted for age, sex, socioeconomic status, smoking, alcohol frequency, body mass index and physical activity

Table S2. Odds ratios (with 95% CI) for the presence of multimorbidity or polypharmacy

Outcome	Self-report COPD compared with no COPD N=502,640		GOLD COPD compared with no COPD N=496,943	
	Model 1 N=502,013	Model 2 N=487,718	Model 1 N=496,324	Model 2 N=482,378
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Multimorbidity (≥4 conditions)	3.49 (3.28-3.70) ***	2.79 (2.61-2.98) ***	2.34 (2.10-2.63) ***	1.99 (1.75-2.25) ***
Polypharmacy (≥5 medications)	3.85 (3.68-4.03) ***	3.30 (3.15-3.46) ***	3.47 (3.20-3.75) ***	3.20 (2.95-3.48) ***
Polypharmacy (≥10 medications)	5.72 (5.36-6.10) ***	4.42 (4.11-4.75) ***	4.20 (3.72-4.73) ***	3.56 (3.12-4.05) ***

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
 Model 1: Adjusted for age, sex and socioeconomic status
 Model 2: Adjusted for age, sex, socioeconomic status, smoking, alcohol frequency, body mass index and physical activity

Table S3. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs

ADR	Self-report COPD compared with no COPD N=502,640		GOLD COPD compared with no COPD N=496,943	
	Model 1 N=502,013	Model 2 N=487,718	Model 1 N=496,943	Model 2 N=482,378
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Falls	2.27 (2.13 – 2.42) ***	1.83 (1.71-1.96) ***	1.66 (1.47 – 1.87) ***	1.49 (1.30-1.69) ***
Constipation	2.71 (2.54 – 2.89) ***	2.66 (2.39-2.96) ***	2.18 (1.77 – 2.64) ***	1.82 (1.47-2.24) ***
Urinary retention	3.38 (2.94 – 3.87) ***	2.59 (2.22-3.0) ***	1.98 (1.44 – 2.64) ***	1.64 (1.18-2.21) **
CNS Depression	3.75 (3.31 – 4.25) ***	2.81 (2.45-3.22) ***	2.29 (1.73 – 2.95) ***	1.87 (1.40-2.43) ***
Bleeding	4.60 (3.35 – 6.19) ***	3.39 (2.40-4.66) ***	2.63 (1.25 – 4.80) **	1.76 (0.75-3.48) §
Renal injury	2.22 (1.86 – 2.62) ***	1.84 (1.53-2.19) ***	1.94 (1.41 – 2.58) ***	1.84 (1.33-2.49) ***

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
 Model 1: Adjusted for age, sex and socioeconomic status
 Model 2: Adjusted for age, sex, socioeconomic status, smoking, alcohol frequency, body mass index and physical activity

Subgroup analyses – comparing COPD with no COPD among participants with specific categories of comorbidity

Table S4. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with cardiovascular disease (CVD)

ADR	Self-report COPD plus CVD compared with CVD alone (no COPD) N=156,848	GOLD COPD plus CVD compared with CVD alone (no COPD) N=154,047
	Model 1 N=156,667	Model 1 N=153,852
	OR (95% CI)	OR (95% CI)
Falls	1.92 (1.79-2.07) ***	1.59 (1.39-1.82) ***
Constipation	2.89 (2.58-3.23) ***	2.06 (1.63-2.57) ***
Urinary retention	2.78 (2.33-3.28) ***	1.92 (1.30-2.72) ***
CNS Depression	3.17 (2.71-3.69) ***	2.17 (1.54-2.97) ***
Bleeding	4.00 (2.85-5.48) ***	2.26 (0.96-4.44) *
Renal injury	1.90 (1.59-2.25) ***	1.82 (1.31-2.45) ***

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
Model 1: Adjusted for age, sex and socioeconomic status

Table S5. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with cancer

ADR	Self-report COPD plus cancer compared with cancer alone (no COPD) N=38,623	GOLD COPD plus cancer compared with cancer alone (no COPD) N=37,958
	Model 1 N=38,575	Model 1 N= 37,912
	OR (95% CI)	OR (95% CI)
Falls	2.35 (1.95-2.81) ***	1.49 (1.00-2.13) *
Constipation	3.55 (2.73-4.56) ***	2.21 (1.22-3.68) **
Urinary retention	3.65 (2.52-5.13) ***	1.99 (0.78-4.14) §
CNS Depression	3.74 (2.66-5.14) ***	2.04 (0.86-4.04) §
Bleeding	4.69 (1.91-9.86) ***	2.20 (0.12-10.23) §
Renal injury	2.0 (1.17-3.20) **	2.26 (0.89-4.71) §

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
Model 1: Adjusted for age, sex and socioeconomic status

Table S6. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with gastrointestinal disease (GI)

ADR	Self-report COPD plus GI compared with GI alone (no COPD) N=58372	GOLD COPD plus GI compared with GI alone (no COPD) N=57103
	Model 1 N=58,299	Model 1 N=57,031
	OR (95% CI)	OR (95% CI)
Falls	2.18 (1.92-2.46) ***	1.46 (1.13-1.87) **
Constipation	2.70 (2.29-3.16) ***	1.58 (1.08-2.24) *
Urinary retention	2.64 (2.12-3.26) ***	1.46 (0.83-2.37) §
CNS Depression	3.02 (2.47-3.66) ***	1.50 (0.88-2.37) §
Bleeding	3.88 (2.27-6.25) ***	3.18 (0.97-7.63) §
Renal injury	1.99 (1.37-2.80) ***	1.22 (0.48-2.51) §

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
Model 1: Adjusted for age, sex and socioeconomic status

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ADR	Self-report COPD plus MH compared with MH alone (no COPD) N=36,949	GOLD COPD plus MH compared with MH alone (no COPD) N=36126
	Model 1 N=36,885	Model 1 N=36,065
	OR (95% CI)	OR (95% CI)
Falls	2.21 (1.90-2.56) ***	1.35 (0.99-1.82) §
Constipation	2.33 (1.93-2.81) ***	1.62 (1.08-2.34) *
Urinary retention	2.17 (1.71-2.74) ***	1.42 (0.82-2.29) §
CNS Depression	2.53 (2.04-3.12) ***	1.66 (1.03-2.54) *
Bleeding	2.86 (1.77-4.17) ***	1.94 (0.76-4.05) §
Renal injury	1.86 (1.19-2.79) **	1.27 (0.45-2.80) §

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
Model 1: Adjusted for age, sex and socioeconomic status

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ADR	Self-report COPD plus painful conditions compared with painful conditions alone (no COPD) N=83,992	GOLD COPD plus painful conditions compared with painful conditions alone (no COPD) N=82,388
	Model 1 N=83,895	Model 1 N=82,294
	OR (95% CI)	OR (95% CI)
Falls	1.99 (1.79-2.21) ***	1.52 (1.23-1.85) ***
Constipation	2.57 (2.22-2.96) ***	1.63 (1.19-2.20) **
Urinary retention	2.47 (2.01-3.00) ***	1.19 (0.69-1.89) §
CNS Depression	2.77 (2.30-3.31) ***	1.48 (0.93-2.22) §
Bleeding	4.23 (2.80-6.14) ***	2.36 (0.84-5.20) §
Renal injury	1.67 (1.29-2.13) ***	1.46 (0.87-2.27) §

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
Model 1: Adjusted for age, sex and socioeconomic status

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	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6,9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
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	6-8
Bias	9	Describe any efforts to address potential sources of bias	14,15
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7,8,9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8-10
		(b) Describe any methods used to examine subgroups and interactions	9,10
		(c) Explain how missing data were addressed	10
		(d) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	9,10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11, figure 1
		(b) Give reasons for non-participation at each stage	11, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	11-13, figure 2, appendix 3
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	11-13, figure 2, appendix 3
		(b) Report category boundaries when continuous variables were categorized	12,13
		(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	12,13, Appendix 3,
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	14,15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15,16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15,16,17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17,18

*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.

BMJ Open

Examining Patterns of Multimorbidity, Polypharmacy and Risk of Adverse Drug Reactions in Chronic Obstructive Pulmonary Disease: A Cross-Sectional UK Biobank Study

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Secondary Subject Heading:	General practice / Family practice
Keywords:	Multimorbidity, Polypharmacy, Chronic airways disease < THORACIC MEDICINE, Adverse events < THERAPEUTICS

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1 **Examining Patterns of Multimorbidity, Polypharmacy and Risk of Adverse Drug Reactions in**

2 **Chronic Obstructive Pulmonary Disease: A Cross-Sectional UK Biobank Study**

3

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20 **Word count: 3446**

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3 21 **Abstract**
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6 22 **Objective:** This study aims: (1) to describe the pattern and extent of multimorbidity and
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8 23 polypharmacy in UK Biobank participants with chronic obstructive pulmonary disease (COPD); and
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10 24 (2) to identify which comorbidities are associated with increased risk of adverse drug reactions
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12 25 (ADRs) resulting from polypharmacy.
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15 26 **Design:** Cross-sectional.
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18 27 **Setting:** Community cohort.
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21 28 **Participants:** UK Biobank participants comparing self-reported COPD (n=8317) with no COPD
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23 29 (n=494,323).
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26 30 **Outcomes:** Multimorbidity (\geq four conditions) and polypharmacy (\geq five medications) in participants
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28 31 with COPD versus those without. Risk of ADRs (taking \geq three medications associated with falls,
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30 32 constipation, urinary retention, central nervous system (CNS) depression, bleeding or renal injury) in
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32 33 relation to the presence of COPD and individual comorbidities.
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34
35 34 **Results:** Multimorbidity was more common in participants with COPD than those without (17% vs.
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37 35 4%). Polypharmacy was highly prevalent (52% with COPD taking \geq five medications vs 18% in those
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39 36 without COPD). Adjusting for age, sex and socioeconomic status, those with COPD were significantly
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41 37 more likely than those without to be prescribed \geq 3 medications contributing to falls (Odds ratio (OR)
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43 38 2.27, 95% confidence interval (CI) 2.13 to 2.42), constipation (OR 3.42, 95% CI 3.10 to 3.77), urinary
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45 39 retention (OR 3.38, 95% CI 2.94 to 3.87), CNS depression (OR: 3.75, 95% CI 3.31 to 4.25), bleeding
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47 40 (OR 4.61, 95% CI 3.35 to 6.19) and renal injury (OR 2.22, 95% CI 1.86 to 2.62). Concomitant
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49 41 cardiovascular disease was associated with the greatest risk of taking \geq 3 medications associated with
50
51 42 falls/renal injury. Concomitant mental health conditions were most strongly associated with
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53 43 medications linked with CNS depression/urinary retention/bleeding.
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56 44 **Conclusions:** Multimorbidity is common in COPD and associated with high levels of polypharmacy.
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59 45 Co-prescription of drugs with various ADRs is common. Future research should examine the effects
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3 46 on healthcare outcomes of co-prescribing multiple drugs with similar potential ADRs. Clinical
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5 47 guidelines should emphasise assessment of multimorbidity and ADR risk.
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13 50 **Abstract word count: 300**
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22 53 **Strengths and Limitations**

- 25 54 • This paper assesses multimorbidity, polypharmacy and risk of adverse drug reactions are
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27 55 assessed in UK Biobank participants with self-reported COPD compared with those without
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29 56 COPD.
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31 57 • Baseline variables from the UK Biobank assessment centre were used to adjust for potential
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33 58 confounders.
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35 59 • Cumulative risk of common adverse drug reactions was quantified by identifying UK Biobank
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37 60 participants taking three or more medications associated with similar adverse drug
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39 61 reactions.
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41 62 • Analyses were repeated using a subgroup of participants with spirometry data confirming
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43 63 airflow obstruction.
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45 64 • Medication and comorbidity data rely on participant self-report, and may thus be
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47 65 susceptible to bias or inaccuracy.
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68 BACKGROUND

69 In people with Chronic Obstructive Pulmonary Disease (COPD), multimorbidity (the presence of two
70 or more long-term conditions (LTCs)) is highly prevalent.(1-4) A recent meta-analysis of 29 datasets
71 demonstrated that those with COPD are significantly more likely to be diagnosed with a range of
72 cardiovascular comorbidities than those without COPD (we will use the term comorbidity when
73 referring to specific conditions in addition to COPD, and multimorbidity to refer to the presence of
74 two or more LTCs).(5) Other LTCs with known increased prevalence in COPD include obesity,(6)
75 depression,(7-10) gastro-oesophageal reflux disease,(11-13) osteoporosis,(14-16) and lung
76 cancer.(17, 18) Each of these conditions has been associated with poorer health related outcomes in
77 COPD when compared to those with no comorbidity.(19-30) The overall burden of multimorbidity
78 also impacts prognosis in COPD, for example higher number of comorbidities is associated with
79 higher risk of mortality,(31) and higher burden of morbidity assessed using the Charlson index and
80 the COPD-specific comorbidity test (COTE) is associated with higher risk of all-cause and respiratory
81 specific mortality.(32, 33) The importance of considering the impact of multimorbidity in the
82 management of long-term conditions is increasingly recognised, however an immature evidence
83 base means that disease specific guidelines often lack specific recommendations with respect to
84 multimorbidity.(34) The prevalence and prognostic significance of multimorbidity in COPD make it a
85 potentially useful exemplar condition in which to consider the specific implications of different
86 patterns of multimorbidity. Polypharmacy is one such implication.

87

88 Multimorbidity in the general population is associated with polypharmacy (often defined as
89 concomitant use of ≥ 5 or ≥ 10 pharmacological agents).(35) Polypharmacy has been associated with
90 increased risk of adverse drug reactions (ADRs)(36-38) and potentially preventable hospital
91 admissions, particularly in the elderly.(39, 40) It has been demonstrated that diagnosis of COPD is
92 associated with increased risk of polypharmacy.(41, 42) This is, in large measure, due to the high

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3 93 burden of extra-pulmonary comorbidities.⁽⁴³⁾ However, little is known about the risk of ADRs in the
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5 94 context of multimorbidity in COPD.
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10 96 Given the well-established burden of multimorbidity and polypharmacy in COPD, it is likely that
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12 97 those with COPD are at increased risk of ADRs resulting from polypharmacy. Previous analyses have
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14 98 not focused on the risk of specific ADRs, or assessed which LTCs increase this risk, instead reporting
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16 99 overall counts of prescribed medication. Data collected for the UK Biobank cohort offers an
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18 100 opportunity to assess how multimorbidity in COPD relates to polypharmacy and to assess the
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20 101 prevalence of co-prescription of medications with similar ADRs.
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27 103 This paper aims:

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30 104 • To describe the pattern and extent of multimorbidity and polypharmacy in UK Biobank
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32 105 participants with COPD.
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34 106 • To identify which LTCs in people with COPD are associated with increased risk of ADRs
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36 107 resulting from polypharmacy.
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3 109 **METHODS**

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6 110 **Data collection**

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8 111 The UK Biobank is a large, population cohort that recruited voluntary participants from throughout
9
10 112 the United Kingdom. Between 2006 and 2010, UK Biobank recruited 502,640 participants aged 37 to
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12 113 73. Participants underwent baseline assessments at one of 22 assessment centres throughout
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14 114 England, Scotland and Wales. Sociodemographic and lifestyle details were recorded using
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16 115 touchscreen questionnaires. Townsend scores were derived from participant postcodes to provide
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18 116 an area-based measure of socioeconomic deprivation. Self-reported LTCs, prescribed and over-the-
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20 117 counter medications, smoking status (current, previous or never) and frequency of alcohol intake
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22 118 (never / special occasions only, one-three times a month, at least once a week) were recorded from
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24 119 a touchscreen questionnaire and subsequent verbal interview with a study nurse. Physical activity
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26 120 was self-reported based on a questionnaire administered in the UK Biobank assessment centre
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28 121 <http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=6164>. We classified the responses into: none (no
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30 122 physical activity in the last four weeks), low (light 'DIY' activity only in the last four weeks), medium
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32 123 (heavy DIY and/or walking for pleasure and/or other exercises in the last four weeks), and high
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34 124 (strenuous sports in the last four weeks).

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38 125 Study centre staff also collected physical measures including height and weight (to calculate body
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40 126 mass index (BMI)) and spirometry. Spirometry was performed using a Vitalograph Pneumotrac 6800.
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42 127 Individual reasons for contraindications to attempting spirometry were not recorded but, according
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44 128 to protocol, these included chest infection in the last month, history of collapsed lung, and heart
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46 129 attack or surgery in the past three months. Full details of the Biobank spirometry protocol are
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48 130 available at <https://biobank.ctsu.ox.ac.uk/crystal/docs/Spirometry.pdf>. In brief, participants were
49
50 131 allowed up to three attempts to provide two reproducible spirometry measurements. Where the
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52 132 reproducibility of the first two was deemed acceptable (<5% variation in both FEV1 and FVC) a third
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54 133 measurement was not performed. All values were recorded along with any error messages
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3 134 generated. As per the American Thoracic Society/European Respiratory Society (ATS/ERS) end-of-
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5 135 test criteria, we interpreted as valid any measurement with no error message or if 'user accepted'
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7 136 was specified.(44) No post-bronchodilator measurements were recorded, which deviates from the
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9 137 ATS/ERS guidelines and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines
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11 138 for COPD.(45, 46)

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14 139 Participants provided full informed consent to participate in UK Biobank and this study had full
15
16 140 ethical approval from the NHS National Research Ethics Service for UK Biobank studies (Ref
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18 141 16/NW/0274); this study is part of UK Biobank approved project number 14151.
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22 23 24 143 **Defining COPD**

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27 144 Participants reporting to have been diagnosed with chronic obstructive pulmonary disease, chronic
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29 145 bronchitis, or emphysema at the nurse-led interview were coded as having 'self-reported COPD'.

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32 146 Due to the potential inaccuracies of using self-reported diagnoses, we identified a subset of those
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34 147 with self-reported COPD who met an adaptation of the Global Initiative for Obstructive Lung Disease
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36 148 (GOLD) spirometry criteria for COPD.(46) This subset, referred to as 'GOLD COPD', was used as a
37
38 149 sensitivity analysis for self-reported COPD, and to stratify findings by severity of airflow obstruction.

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40 150 For participants with self-report COPD and valid spirometry measurements, we calculated the ratio
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42 151 of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) using the highest
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44 152 measurement for each participant meeting the American Thoracic Society/European Respiratory
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46 153 Society end-of-test criteria.(44) Those with a FEV1/FVC ratio <0.7 were classed as having an
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48 154 obstructive deficit and thus meeting the GOLD diagnostic criteria for COPD. We used the Hankinson
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50 155 equation,(47) based on recorded age, sex and height, to calculate predicted FEV1 values for each
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52 156 participant. Those with GOLD COPD were classified on the basis of their best available FEV1
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3 157 measurement as having mild (>80% predicted FEV1), moderate (50-80% predicted FEV1), or severe
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5 158 (<50% predicted FEV1) airflow obstruction in line with the GOLD COPD guidelines.(46)
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10 160 **Defining long term conditions and medications**

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13 161 All LTCs were defined by self-report. The list of included LTCs was taken from a list of 42 morbidities
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15 162 originally established for a large multimorbidity epidemiological study in Scotland, through
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17 163 systematic review, the Quality and Outcomes Framework, NHS Scotland and an expert panel (48),
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19 164 and subsequently amended for UK Biobank (49). The inclusion of 'other painful conditions'
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21 165 comprised LTCs in which pain is a predominant feature (particularly as this is likely to influence
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23 166 medication use). It should be noted that such a list is not exhaustive, but intended to cover common
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25 167 conditions frequently requiring prescription of analgesics (e.g. osteoarthritis, back pain, headaches
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27 168 etc.). Morbidities were categorised for the purposes of this analysis into cardiovascular disease,
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29 169 gastrointestinal disease, mental health conditions, cancer, and painful conditions/inflammatory
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31 170 arthropathies (comprising the list of 'other painful conditions' mentioned above, plus connective
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33 171 tissue diseases). Full details of conditions comprising each category can be found in appendix 1.
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36
37 172 Medication data were collected by self-report. Medications were coded by mechanism of action
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39 173 according to the British National Formulary (BNF) (e.g. Angiotensin-converting enzyme inhibitors,
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41 174 beta-blockers, calcium channel blockers, etc.). For some situations where more than one medication
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43 175 with a similar mechanism of action may be commonly co-prescribed (e.g. aspirin and clopidogrel,
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45 176 both antiplatelets) these were coded separately. A complete list of the medications coded within
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47 177 each class can be found in appendix 2.
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51 178 We defined those at risk of specific ADRs as anyone on 3 or more medications with similar potential
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53 179 ADRs, based on information provided in the *Scottish Government Model of Care Polypharmacy*
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55 180 *Working Group: Polypharmacy Guidance*.(50) This guideline cross-tabulates commonly prescribed
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3 181 medications with common ADRs to help identify those at cumulative risk of ADRs. This document
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5 182 groups common medications by similar potential ADRs. While this list is not all-inclusive, and the cut-
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7 183 off value of three or more medications is arbitrary, this does allow an estimation of the cumulative
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9 184 risk of specific ADRs. We identified six potential ADRs (falls/fractures, constipation, urinary
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11 185 retention, CNS depression, bleeding and renal injury) for which the proportion of participants taking
12
13 186 three or more associated medications could be assessed. It should be noted that several of these
14
15 187 event (e.g. falls/fractures, CNS depression) are often multifactorial, and medication may be a
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17 188 contributing factor rather than a definitive cause. As the guideline acknowledges, however, these
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19 189 are clinical events of which the risk is increased by taking multiple associated medications.
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25 191 **Statistical analysis**

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28 192 Study hypothesis was made an analyses planned prior to inspection of the data.
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31 193 **Baseline variables**

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34 194 Comparisons were made between participants with self-reported COPD and the rest of the cohort
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36 195 (who did not report COPD). Age, sex, smoking status, deprivation (Townsend score), BMI, physical
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38 196 activity and frequency of alcohol intake were compared using χ^2 test for categorical variables, χ^2 test
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40 197 for trend for ordinal variables, and Mann-Whitney-U test for continuous variables. Total number of
41
42 198 morbidities, prevalence of specific morbidities, number of self-reported prescribed medications, and
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44 199 proportion of participants taking each class of medication (Appendix 2), were also compared
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46 200 between those with self-reported COPD and the rest of the cohort. All comparisons were repeated
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48 201 comparing participants with GOLD COPD only with those without COPD, stratifying by severity of
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50 202 airflow obstruction.
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53 203 **Multimorbidity and polypharmacy**

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3 204 Logistic regression analyses were used to compare participants with self-reported COPD and those
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5 205 without COPD. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for:

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8 206 • the presence of cardiovascular disease, cancer, gastrointestinal disease, mental health
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10 207 conditions and painful conditions/inflammatory arthropathies
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12 208 • the presence of four or more morbidities (excluding COPD)
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14 209 • the use of five or more, and 10 or more, medications (two separate models)
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17 210 Models were initially adjusted for age, sex and socioeconomic deprivation (model 1), then adjusted
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19 211 for the addition of smoking status, alcohol frequency, BMI and physical activity (model 2). These
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21 212 analyses were repeated comparing those with GOLD COPD only to those without COPD.
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23 24 213 **Risk of ADRs**

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27 214 For each potential ADR (falls/fractures, constipation, urinary retention, CNS depression, bleeding
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29 215 and renal injury) participants taking three or more medications associated with that ADR were
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31 216 identified. The following comparisons were then made:

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34 217 • Unadjusted percentages at risk of each ADR were calculated for participants without COPD,
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36 218 with self-reported COPD, and with self-reported COPD plus each category of LTC
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38 219 (cardiovascular disease, cancer, gastrointestinal disease, mental health conditions and
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40 220 painful conditions/inflammatory arthropathies) to give an impression of the ADR risk in
41
42 221 COPD, and identify LTCs in those with COPD that may increase this risk.
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44 222 • ORs of being at risk of each ADR were calculated comparing those with self-reported COPD
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46 223 to those without COPD adjusting for age, sex and socioeconomic deprivation (model 1) and
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48 224 for age, sex, socioeconomic deprivation, smoking status, alcohol frequency, BMI and physical
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50 225 activity (model 2).
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52 226 • ORs of being at risk of each ADR were calculated comparing those with and without self-
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54 227 reported COPD in each LTC category to (i.e. participants with cardiovascular disease alone
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3 228 compared to participants with cardiovascular disease plus COPD, etc.). This was intended to
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5 229 identify whether specific patterns of multimorbidity in COPD are associated with increased
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7 230 ADR risk. Adjustment for a wide range of potential confounders was not appropriate in
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9 231 these models due to the smaller number of participants in each model.

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12 232 Each analysis was repeated comparing GOLD COPD only to those without COPD. Less than 3% of
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14 233 participants (with or without COPD) had missing data for potential confounding variables (table 1).
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16 234 Those with missing data were excluded from adjusted analyses. Spirometry data were missing for
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18 235 3591 participants with self-report COPD (43%), hence the use of the GOLD COPD subset as a
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20 236 sensitivity analysis.

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23 237 All analyses were performed using R statistical software (version 3.3.1).
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3 240 **RESULTS**
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6 241 At the time of recruitment, 8317 out of 502,619 participants reported having COPD (1.7%) and are
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8 242 referred to here as the self-report COPD group. Of those who self-reported COPD, 4726 (57%) had
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10 243 valid spirometry measurements. Spirometry was contraindicated or not available in 2507 of those
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12 244 with self-reported COPD. Spirometry measurements did not meet the ATS/ESR end-of-test criteria in
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14 245 1084 participants.(44) Of those with valid spirometry, 2620 (55%) met the GOLD criteria for airflow
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16 246 obstruction (399 (15%) mild, 1409 (54%) moderate, 812 (31%) severe, see Figure 1) and are referred
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18 247 to here as GOLD COPD.
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24 249 **Baseline variables**
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26
27 250 Table 1 describes and compares the characteristics of those with and without COPD in UK Biobank.
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29 251 Participants with COPD (both self-report and GOLD) were significantly older, more socioeconomically
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31 252 deprived, and less physically active. A higher proportion of those with COPD were male, obese and
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33 253 had a history of smoking.
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Table 1. Baseline variables								
Characteristic	No COPD n=494323		COPD (self-report) n=8317			GOLD GOPD n=2620		
	Count	%	Count	%	p-value	Count	%	p-value
Sex								
Male	224906	45.5	4268	51.3		1426	54.4	
Female	269417	54.5	4049	48.7	<0.001	1194	45.6	<0.001
Age	Median: 58 IQR: 50-63		Median: 62 IQR: 57-66		<0.001	Median: 63 IQR: 59-66		<0.001
Ethnicity								
White	464770	94.5	8052	97.3		2620	100	
Other	26821	5.4	219	2.6	<0.001	0	0	<0.001
Missing	2732		46			0	0	
Socioeconomic deprivation quintile								
1 (least deprived)	99672	20.2	1015	12.2		309	11.8	
2	98977	20.0	1142	13.7		362	13.8	
3	99013	20.1	1399	16.8		440	16.8	
4	98660	20.0	1735	20.9		580	22.2	
5 (most deprived)	98385	19.7	3015	36.3	<0.001	926	35.4	<0.001
Missing	616		11			3		
Smoking status								
Current	50817	10.3	2172	26.3		833	32.2	
Previous	169015	34.4	4083	49.5		1398	54.0	
Never	271602	55.3	1999	24.2	<0.001	360	13.9	<0.001
Missing	2889		63			29		
Alcohol frequency								
Daily	100070	20.3	1720	20.7		618	23.6	
3-4 times/week	114058	23.1	1404	16.9		475	18.2	
1-2 times/week	127459	25.9	1863	22.5		561	21.5	
1-3 times/month	54979	11.2	894	10.8		289	11.1	
Occasional	56707	11.5	1322	15.9		387	14.8	<0.001
Never	39569	8.0	1092	13.2	<0.001	284	10.9	
Missing	1481		22			6		
BMI								
<18.5	2478	0.5	148	1.8		56	2.2	
18.5-24.9	155282	31.8	2185	26.8		829	31.9	
25.0-29.9	211102	43.2	3165	38.9		1049	40.4	
>30	119813	24.5	2647	32.5	<0.001	665	25.6	<0.001
Missing	5648		172			21		
Physical activity								
High	49827	10.6	250	3.1		70	2.7	
Medium	387766	79.6	5838	72.0		1902	73.3	
Low	18354	3.8	589	7.3		203	7.8	
None	31425	6.4	1433	17.7	<0.001	421	16.2	<0.001
Missing	6951		207			24		
FEV1 (% predicted)								
>80	272109	78.0	1853	39.2		399	15.2	
50-79	71727	20.6	2022	42.8		1409	53.8	
<50	4841	1.4	851	18.0	<0.001	812	31.0	<0.001
Missing	145646		3591			1061		

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3 **256 Multimorbidity and polypharmacy**
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6 257 Prevalence of each category of comorbidity was higher in those with COPD than without (table 2).
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8 258 After controlling for age, sex and socioeconomic status, those with self-reported COPD were
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10 259 significantly more likely than those without to have each category of LTC examined: cardiovascular
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12 260 disease (OR 1.45; 95% confidence interval (CI) 1.39 to 1.52) , cancer (1.29; 1.2 to 1.39),
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14 261 gastrointestinal disease (1.76; 1.67 to 1.86) , mental health conditions (2.02; 1.89 to 2.15) , and
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16 262 painful conditions (1.54; 1.46 to 1.62). Results for GOLD COPD also suggested higher likelihood of
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18 263 each LTC compared to those without COPD, although the ORs were lower and results for cancer not
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20 264 statistically significant (appendix 3). Results were similar after adjusting for additional confounders
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22 265 (smoking status, alcohol frequency, BMI and physical activity) with the exception of cardiovascular
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24 266 disease in GOLD COPD, which was no longer significantly associated (1.08; 0.99 to 1.18) (appendix 3).
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Table 2: Long Term Conditions in those with and without COPD						
	Control n=494323 count (%)	Self-report COPD n=8317 count (%)	GOLD COPD			
			All n=2620 count (%)	Mild n=399 count (%)	Moderate n=1409 count (%)	Severe n= 812 count (%)
Total comorbidities (excluding COPD) ≥ 4	19959 (4.0)	1389 (16.7)**	331 (12.6)**	46 (11.5)	191 (13.5)	94 (11.6)
Total number of medications ≥ 1	356406 (72.1)	7670 (92.2)**	2452 (93.6)**	352 (88.2)	1321 (93.8)	779 (95.9)
≥ 5	87286 (17.7)	4312 (51.8)**	1349 (51.5)**	171 (42.9)	702 (49.8)	476 (58.6)
≥ 10	10678 (2.2)	1269 (15.3)**	329 (12.6)**	31 (7.8)	172 (12.2)	126 (15.5)
Prevalence of comorbidities						
Cardiovascular	152891 (30.9)	3957 (47.6)**	1156 (44.1)**	142 (35.6)	611 (43.4)	403 (49.6)
Hypertension	130119 (26.3)	3206 (38.5)**	916 (35.0)**	112 (28.1)	483 (34.3)	321 (39.5)
CHD	21560 (4.4)	1171 (14.1)**	315 (12.0)**	31 (7.6)	185 (13.1)	99 (12.2)
Diabetes	24737 (5.0)	766 (9.1)**	189 (7.2)**	16 (4.0)	109 (7.7)	64 (7.9)
Stroke/TIA	8459 (1.7)	395 (4.7)**	98 (3.7)**	11 (2.8)	51 (3.6)	36 (4.4)
AF	3552 (0.7)	99 (1.2)**	34 (1.3)**	3 (0.8)	16 (1.1)	15 (1.8)
Heart failure	768 (0.2)	35 (0.4)**	6 (0.2)	0	1 (0.1)	5 (0.6)
Respiratory						
Asthma	55245 (11.2)	3048 (36.6)**	984 (37.6)**	142 (35)	523 (37.1)	319 (39.3)
PE/DVT	12316 (2.5)	554 (6.7)**	139 (5.3)**	29 (7.3)	71 (5.0)	39 (4.8)
Bronchiectasis	968 (0.2)	167 (2.0)**	39 (1.5)**	7 (1.8)	17 (1.2)	15 (1.8)
Pulmonary fib.	504 (0.1)	67 (0.8)**	18 (0.7)**	3 (0.8)	12 (0.9)	3 (0.4)
Cancer	37686 (7.6)	937 (11.3)	272 (10.4)	47 (11.8)	146 (10.4)	79 (9.7)
Lung	405 (0.1)	52 (0.6)**	15 (0.6)**	0	7 (0.5)	8 (1.0)
Breast	11311 (2.3)	210 (2.5)*	57 (2.2)	12 (3.0)	30 (2.1)	15 (1.8)
Prostate	3588 (0.7)	105 (1.3)**	30 (1.1)*	5 (1.3)	12 (0.9)	13 (1.6)
GI	2925 (0.6)	96 (1.2)**	34 (1.3)**	6 (1.5)	19 (1.3)	9 (1.1)
Haem	6170 (1.2)	124 (1.5)*	34 (1.3)	5 (1.3)	17 (1.2)	12 (1.5)
Gastrointestinal	55635 (11.5)	1737 (20.9)**	468 (17.9)**	76 (19.0)	254 (18.0)	138 (17.0)
Dyspepsia	37819 (7.7)	1257 (15.1)**	348 (13.3)**	53 (13.3)	189 (13.4)	106 (13.1)
Diverticular dis	5181 (1.0)	224 (2.7)**	54 (2.1)**	6 (1.5)	32 (2.3)	16 (2.0)
IBS	11203 (2.3)	291 (3.5)**	64 (2.4)**	17 (4.3)	35 (2.5)	12 (1.5)
CLD	935 (0.2)	36 (0.4)**	10 (0.4)*	2 (0.5)	10 (0.7)	3 (0.4)
Mental Health	35822 (7.2)	1127 (13.6)**	304 (11.6)**	54 (13.5)	162 (11.5)	88 (10.8)
Depression	27578 (5.6)	901 (10.8)**	233 (8.9)**	42 (10.5)	128 (9.1)	63 (7.8)
Anxiety	8781 (1.8)	245 (2.9)**	69 (2.6)**	13 (3.3)	36 (2.6)	20 (2.5)
Schizophrenia/ bipolar	1918 (0.4)	79 (0.9)**	27 (1.0)**	3 (0.7)	15 (1.1)	9 (1.1)
Other						
Other painful	81733 (16.5)	2259 (27.2)**	655 (25.0)**	115 (28.8)	367 (26.0)	173 (21.3)
Osteoporosis	7700 (1.6)	342 (4.1)**	128 (4.9)**	21 (5.3)	67 (4.8)	40 (4.9)
Connective tissue disease	10642 (2.2)	391 (4.7)**	112 (4.3)**	19 (4.8)	72 (5.1)	21 (2.6)

Compared with control (χ^2): * : p<0.05, ** : p<0.001

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3 270 Morbidity counts (excluding COPD) and counts of prescribed medication are shown in table 2
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5 271 comparing those with COPD, stratified by severity of airflow obstruction, with those without. Those
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7 272 with COPD had higher numbers of LTCs and more prescribed medications than those without. There
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9 273 was a trend towards more prescribed medications in those with greater severity of airway
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11 274 obstruction. After controlling for age, sex and socioeconomic status, those with self- report COPD
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13 275 were more likely to report ≥ 4 LTCs (3.49; 3.28 to 3.71), ≥ 5 medications (3.85; 3.68 to 4.03), and ≥ 10
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15 276 medications (5.72; 5.36 to 6.10) than those without COPD. Results were similar for GOLD COPD and
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17 277 remained statistically significant after adjusting for smoking status, alcohol frequency, BMI and
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19 278 physical activity (appendix 3).

279 **ADR Risk**

25 280 Counts and percentages of participants taking specific medications are shown in appendix 4.
26
27 281 Participants with COPD (self-report and GOLD) were more likely than those without COPD to be
28
29 282 prescribed drugs across a range of disease areas, reflecting the range of LTCs present among those
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31 283 with COPD. The percentages of participants within each category (no COPD, COPD, and COPD with
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33 284 specific LTCs) taking three or more medications associated with a similar ADR is shown in Figure 2.
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35 285 For each category of ADR a higher proportion of participants with COPD reported taking three or
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37 286 more associated medications than those without COPD. This increased further with multimorbidity.
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39 287 Participants with COPD plus cardiovascular disease had the highest percentage taking three or more
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41 288 medications with a risk of falls or renal injury. Participants with COPD plus mental health conditions
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43 289 had the highest percentages taking three or more medications with a risk of constipation, CNS
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45 290 depression or bleeding.

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52 292 After adjusting for age, sex and socioeconomic deprivation, those with self-report COPD remained
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54 293 more likely to be taking three or more medications in each category than those without COPD. These

294 findings remained statistically significant after adjusting for smoking status, alcohol frequency, BMI
 295 and physical activity (Table 3). Findings were similar for GOLD COPD however, after adjusting for
 296 additional potentially confounding variables, results for bleeding risk were not statistically significant
 297 in this sensitivity analysis (Table 3).

Table 3. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs

ADR	Self-report COPD compared with no COPD N=502,640		GOLD COPD compared with no COPD N=496,943	
	Model 1 N=502,013	Model 2 N=487,718	Model 1 N=496,943	Model 2 N=482,378
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Falls	2.27 (2.13 – 2.42) ***	1.83 (1.71-1.96) ***	1.66 (1.47 – 1.87) ***	1.49 (1.30-1.69) ***
Constipation	2.71 (2.54 – 2.89) ***	2.66 (2.39-2.96) ***	2.18 (1.77 – 2.64) ***	1.82 (1.47-2.24) ***
Urinary retention	3.38 (2.94 – 3.87) ***	2.59 (2.22-3.0) ***	1.98 (1.44 – 2.64) ***	1.64 (1.18-2.21) **
CNS depression	3.75 (3.31 – 4.25) ***	2.81 (2.45-3.22) ***	2.29 (1.73 – 2.95) ***	1.87 (1.40-2.43) ***
Bleeding	4.60 (3.35 – 6.19) ***	3.39 (2.40-4.66) ***	2.63 (1.25 – 4.80) **	1.76 (0.75-3.48) §
Renal injury	2.22 (1.86 – 2.62) ***	1.84 (1.53-2.19) ***	1.94 (1.41 – 2.58) ***	1.84 (1.33-2.49) ***

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
 Model 1: Adjusted for age, sex and socioeconomic status
 Model 2: Adjusted for age, sex, socioeconomic status, smoking, alcohol frequency, body mass index and physical activity

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299 Finally, each category of ADR risk was assessed in a subgroup analysis for each category of LTC
 300 (cardiovascular, GI, cancer, mental health and painful conditions/inflammatory arthropathies)
 301 comparing those with and without COPD (e.g. participants with cardiovascular disease plus COPD
 302 compared with participants with cardiovascular disease alone, etc.). These models were adjusted for
 303 age, sex and socioeconomic status only. Within each category of LTC, those with self-reported COPD
 304 were more likely to be at risk of each ADR than those without COPD (appendix 3). Not all results
 305 were statistically significant when using GOLD COPD (Appendix 3).

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3 311 **DISCUSSION**
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6 312 **Summary of main findings**
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9 313 Multimorbidity and polypharmacy in COPD were common among UK Biobank participants. The
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11 314 presence of multimorbidity was highly prevalent in those with COPD (85%). More than half reported
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13 315 polypharmacy (five or more medications), and 15% reported 10 or more medications. The
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15 316 prevalence of cardiovascular disease, as well as the degree of polypharmacy, was higher among
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17 317 those with more severe airflow obstruction.

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20 318 For the first time, our data demonstrates that those with COPD were more likely than those without
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22 319 to be prescribed multiple medications (\geq three) with similar ADRs. Those with COPD plus
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24 320 cardiovascular disease were most likely to be taking multiple medications associated with increased
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26 321 risk of falls or renal injury, while those with COPD plus mental health conditions were most likely to
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28 322 be taking medications predisposing to constipation, CNS depression and bleeding.(50) Within each
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30 323 category of LTC, those with COPD were more likely to be taking multiple medications with similar
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32 324 ADRs than those without. These associations between patterns of multimorbidity and specific ADR
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34 325 risks have not been described or quantified previously.
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40 327 **Strengths and limitations**
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43 328 Strengths of this study include the large sample size with representation from different areas of the
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45 329 UK. The range of data collected at UK Biobank assessment centres meant it was possible to compare
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47 330 a range of sociodemographic characteristics as well as spirometry data, the latter being unusual for a
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49 331 large community based cohort. It is recognised, however, that UK Biobank participants show some
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51 332 evidence of 'healthy volunteer bias', differing from the UK average on a number of socioeconomic,
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53 333 lifestyle and health-related measures. Specifically they are less socioeconomically deprived, less
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55 334 likely to smoke, to be obese, and have fewer self-reported health conditions.(51) All LTC diagnoses
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3 335 as well as medication data were self-reported, with no alternative means of verification. We
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5 336 attempted to minimise this limitation by identifying a subset of those with COPD meeting the GOLD
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7 337 diagnostic criteria and repeating the analyses with this subset. Importantly, spirometry values were
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9 338 also pre-bronchodilator, which is in contravention to guidelines for diagnosing COPD. Additionally,
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11 339 information was not available about the strength of indication for medications and individual
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13 340 susceptibility to risk, which is a limitation when considering the risk of ADRs.

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16 341 The use of the Scottish Government Polypharmacy Guideline allowed analysis of potential ADR risk
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18 342 by specific common ADRs. The intended purpose of this guideline, however, was not to identify
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20 343 potential risk from a population sample, but rather to identify potential causes of symptoms or
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22 344 complications. The analysis in this study, therefore, serves only as an approximation of potential risk,
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24 345 not an absolute marker of inappropriate polypharmacy. The cross-sectional nature of this analysis
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26 346 also precludes an analysis of actual harm as a result of polypharmacy. Many of the potential ADRs,
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28 347 such as falls and fractures and renal injury, and frequently multifactorial events and may not be
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30 348 directly attributable to medication use. Despite these limitations, however, the co-prescription of
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32 349 multiple medications with similar ADRs strongly implies greater potential for harm. The association
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34 350 of such prescribing patterns with COPD, across a range of potential ADRs, is clear from our findings.
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36 351 This analysis is, to the author's knowledge, the first to attempt to quantify this risk for specific ADRs
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38 352 in this way.

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43 44 45 354 **Context and implications**

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48 355 The increased prevalence of individual LTCs such as coronary heart disease, hypertension, diabetes,
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50 356 dyspepsia, osteoporosis, cancer, depression and anxiety in those with COPD is similar to the findings
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52 357 from other population based studies of multimorbidity in COPD.(5, 11, 52-54) Our finding that
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54 358 cardiovascular disease prevalence increased with increasing severity of COPD is in keeping with the

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3 359 body of literature on cardiovascular disease and COPD, in which high prevalence has been observed
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5 360 in (usually older) cohorts with severe airflow limitation.(5, 21) Greater polypharmacy with greater
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7 361 severity of COPD has also been observed previously in older COPD populations,(42, 55) although
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9 362 such analyses have been smaller (n=1859 and 398, respectively) and have not assessed the specific
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11 363 patterns of prescribing in COPD. To the best of our knowledge, no previous studies have assessed
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13 364 the risk of ADRs as a result of polypharmacy in COPD. A recent population-based analysis of
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15 365 prescribing data from 310,000 adults in Scotland showed that over 15 years from 1995 to 2010 the
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17 366 proportion of people with polypharmacy and with potentially serious drug-to-drug interactions
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19 367 increased dramatically.(36) The number of prescribed medications was also associated with
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21 368 increased risk of interactions. Our analysis differs in approach from this analysis, by seeking to
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23 369 identify patterns of prescribing increasing risk of specific adverse events, rather than counting total
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25 370 potential interactions. The strength of our approach lies in highlighting specific patterns of
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27 371 multimorbidity in which specific ADRs are more likely. Our findings can therefore be applied to
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29 372 clinical practice, highlighting the importance of recognising multimorbidity in COPD and being alert
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31 373 to specific ADRs when prescribing medication.
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38 375 Our findings indicate that in those with COPD the potential for ADRs as a result of combinations of
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40 376 medications is high, and this appears to be the result of a high prevalence of extra-pulmonary LTCs.
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42 377 Clinical guidelines for COPD should place greater emphasis on the need for assessment of associated
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44 378 multimorbidity and the risk of associated ADRs. While our analysis shows potential areas where ADR
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46 379 risk exists in COPD (e.g. falls in those with concomitant cardiovascular disease, CNS depression,
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48 380 constipation with concomitant mental health conditions), future research is merited to assess what
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50 381 actual harm could be attributed to such prescribing patterns.
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53 382 **Conclusion**

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3 383 Among UK Biobank participants with COPD there was considerable multimorbidity and
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5 384 polypharmacy. Those with COPD were highly likely to be concurrently prescribed multiple
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7 385 medications with similar potential adverse effects. Medications contributing to this risk were
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9 386 largely indicated for the management of the associated morbidities rather than COPD. Future
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11 387 research should examine the effects on healthcare outcomes of co-prescribing of multiple drugs
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13 388 with similar potential of ADRs. Clinical guidelines for COPD should emphasise the need for
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15 389 assessment of multimorbidity and the risk of associated ADRs.
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391 **Figure Legends**

392 **Figure 1:** Flow diagram of identification of participants with 'self-report COPD' and 'GOLD COPD'.

393 **Figure 2:** Bubble plot showing percentage of participants in each comorbidity category taking 3 or
394 more concomitant medications associated with specific adverse drug reactions.

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397 **Ethics approval and consent to participate**

398 Participants provided full informed consent to participate in UK Biobank and this study was covered
399 by the generic ethical approval for UK Biobank studies from the NHS National Research Ethics
400 Service (Ref 16/NW/0274).

401

402 **Availability of data and materials**

403 UK Biobank data is available via www.ukbiobank.ac.uk. Syntax for the generation of derived
404 variables and for the analysis used for this study will be submitted to UK Biobank for record.

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6 406 **Competing interests**

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8 407 The authors declare that they have no competing interests
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22 412 **Author contributions**

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25 413 All authors (PH, BN, BJ, RM, DL, KG and FM) were involved in the conceptualisation and design of the
26

27 414 project and interpretation of results. PH carried out the analysis with support from BJ, RM and BN.
28

29 415 DL provided statistical support. All authors had access to the data. PH wrote the first draft of the
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31 416 paper and all authors commented on subsequent drafts. All authors approved the final draft for
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33 417 publication. FM is guarantor.
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53 424 **References**
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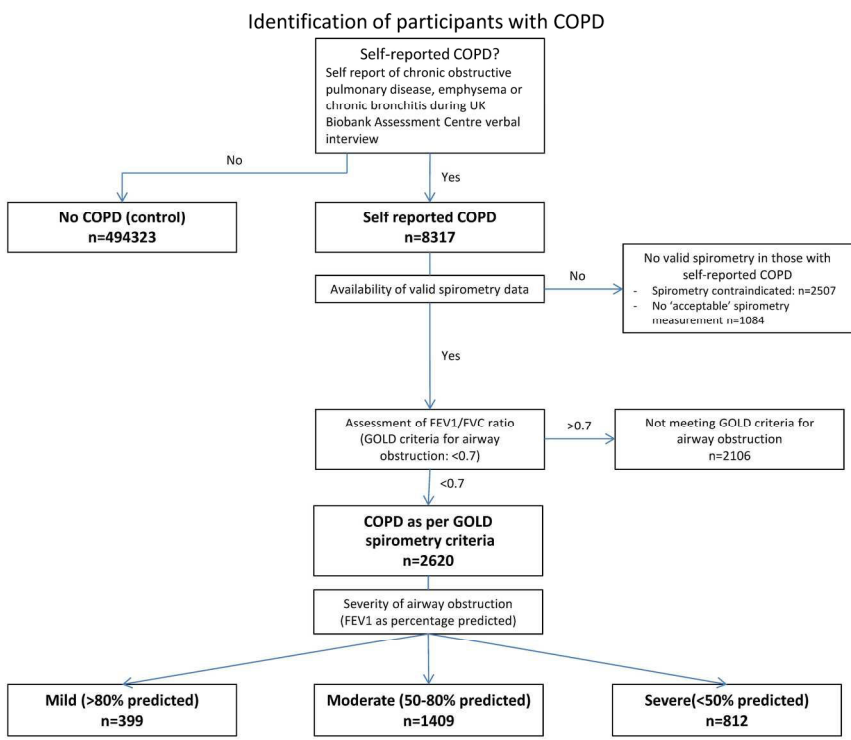
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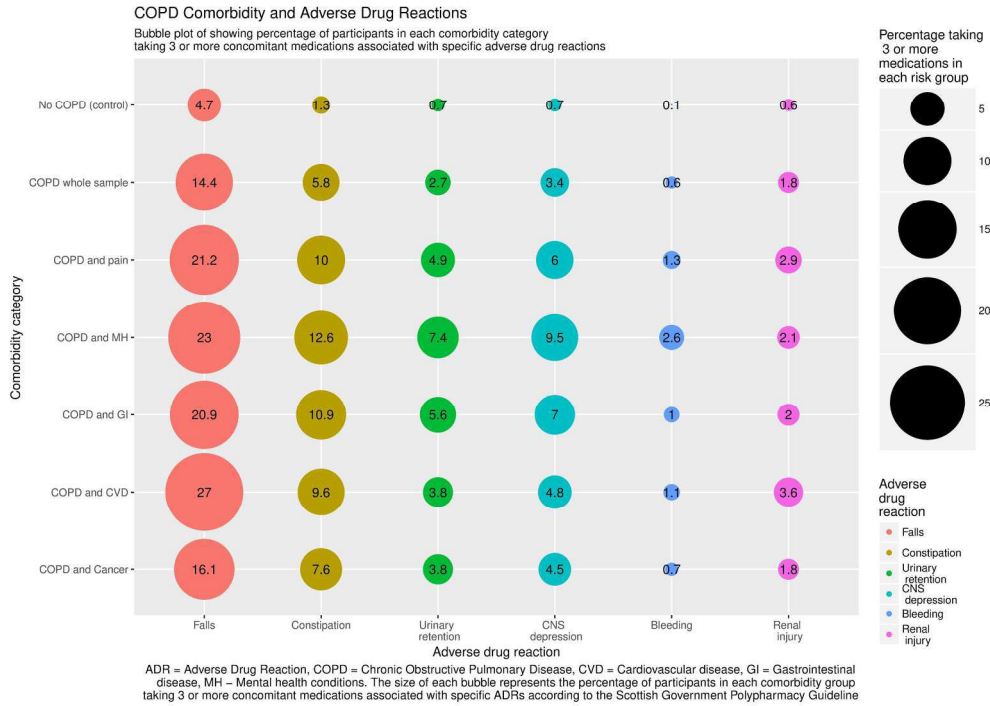
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Flow diagram of identification of participants with 'self-report COPD' and 'GOLD COPD'.

190x142mm (300 x 300 DPI)



Bubble plot showing percentage of participants in each comorbidity category taking 3 or more concomitant medications associated with specific adverse drug reactions.

209x148mm (300 x 300 DPI)

Comorbidity category (used in analysis)	Conditions included (as reported in table 2)	Self-reported conditions comprising this condition (UK Biobank variables used to identify self-reported conditions)
Cardiovascular conditions	Hypertension	Hypertension Essential hypertension
	Coronary heart disease	Heart attack/MI Angina
	Diabetes	Diabetic nephropathy Diabetic neuropathy/ulcers Diabetes Type 1 diabetes Type 2 diabetes Diabetic eye disease
	Stroke/TIA	Stroke TIA Subarachnoid haemorrhage Brain haemorrhage Ischaemic stroke
	Atrial fibrillation	Atrial fibrillation
	Heart failure	Cardiomyopathy Hypertrophic cardiomyopathy Heart failure/pulmonary oedema
	Peripheral vascular disease	Peripheral vascular disease Leg claudication/intermittent claudication
Respiratory	COPD	COPD/Chronic obstructive pulmonary disease Emphysema/Chronic bronchitis Emphysema
	Asthma	Asthma
	PE/DVT	Deep vein thrombosis Pulmonary embolism
	Bronchiectasis	Bronchiectasis
	Pulmonary fibrosis	Pulmonary fibrosis
Cancer	Cancer	"yes"/"no" to "have you ever had cancer?"
Gastrointestinal	Dyspepsia	Gastro-oesophageal reflux (GORD) Oesophagitis/Barrett's oesophagus Gastric stomach ulcers Gastric erosions/gastritis Duodenal ulcer Dyspepsia/indigestion Hiatus hernia Helicobacter pylori
	Diverticular disease	Diverticular disease/diverticulitis

	Irritable bowel syndrome	Irritable bowel syndrome
	Chronic liver disease	Oesophageal varices Non infective hepatitis Liver failure/cirrhosis Primary biliary cirrhosis
	Inflammatory bowel disease	Inflammatory bowel disease Crohn's disease Ulcerative colitis
	Constipation	Constipation
	Viral hepatitis	Hepatitis B Hepatitis C Hepatitis D
Mental Health	Depression	Depression Postnatal depression
	Anxiety	Anxiety/panic attacks Nervous breakdown Post-traumatic stress disorder Obsessive compulsive disorder Stress Insomnia Psychological/psychiatric problem
	Schizophrenia	Schizophrenia
	Bipolar	Mania Bipolar disorder Manic depression
Painful conditions	Connective tissue diseases	Myositis/myopathy Systemic lupus erythematosus/SLE Connective tissue disorder Sjogren's syndrome.sicca syndrome Dermatopolymyositis Scleroderma/systemic sclerosis Rheumatoid arthritis Psoriatic arthropathy Dermatomyositis Polymyositis Polymyalgia rheumatica
	Other painful conditions	Back pain Joint pain Headaches (not migraine) Sciatica Plantar fasciitis Carpal tunnel syndrome Fibromyalgia Arthritis Shingles Disc problem Prolapsed disc/slipped disc

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		Spine arthritis/spondylitis Ankylosing spondylitis Back problem Osteoarthritis Gout Cervical spondylosis Trigeminal neuralgia Disc degeneration Trapped nerve/compressed nerve
Other	Osteoporosis	Osteoporosis

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Drugs with cumulative risk of Adverse Drug Reactions*	
Adverse Drug Reaction	Contributing drug classes (participants taking 3 or more considered 'at risk' for the purposes of analysis)
Falls	H2-receptor blockers Loperamide Prochlorperazine Metoclopramide ACE-inhibitor/Angiotensin receptor blocker Thiazide diuretic Loop diuretic Amiloride/triamterene Spironolactone Beta-blocker Calcium-channel blocker Nitrates or nicorandil Digoxin Oral steroids Opiates Benzodiazepines Sedative antihistamines H1-receptor blockers Antipsychotics Tricyclic antidepressants Sulfonylureas/gliptins/glinides Pioglitazone Urinary antispasmodics Dosulepin Alpha-blockers
Constipation	H2-receptor blockers Laxatives Loperamide Prochlorperazine Thiazide diuretics Loop diuretics Calcium-channel blockers Opiates Sedative antihistamines H1-receptor blockers Antipsychotics Tricyclic antidepressants Urinary antispasmodics Dosulepin
Urinary retention	H2-receptor blockers Loperamide Prochlorperazine Opiates Sedative antihistamines H1-receptor blockers Antipsychotics Tricyclic antidepressants

	Urinary antispasmodics Dosulepin
CNS depression	H2-receptor blockers Loperamide Prochlorperazine Oral steroids Opiates Benzodiazepines Sedative antihistamines H1-receptor blockers Antipsychotics Tricyclic antidepressants Urinary antispasmodics Dosulepin
Bleeding	Aspirin Clopidogrel Other antiplatelets Oral steroids SSRIs and related drugs Non-steroidal anti-inflammatory drugs Warfarin
Renal injury	ACE-inhibitor/angiotensin receptor blockers Thiazide diuretic Loop diuretic Amiloride/triamterene Spironolactone Antibiotics/antifungals Non-steroidal anti-inflammatory drugs
Adapted from <i>Scottish Government Model of Care Polypharmacy Working Group. Polypharmacy Guidance (2nd edition) March 2015. Scottish Government.</i>	

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Comorbidity category	Self-report COPD compared with no COPD N=502,640		GOLD COPD compared with no COPD N=496,943	
	Model 1 N=502,013	Model 2 N=487,718	Model 1 N=496,324	Model 2 N=482,378
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Cardiovascular disease	1.45 (1.39-1.52) ***	1.28 (1.22-1.34) ***	1.11 (1.02-1.20) *	1.08 (0.99-1.18) §
Cancer	1.29 (1.20-1.39) ***	1.22 (1.13-1.31) ***	1.12 (0.99-1.27) §	1.06 (0.92-1.19) §
Gastrointestinal disease	1.76 (1.67-1.86) ***	1.56 (1.48-1.65) ***	1.4 (1.26-1.54) ***	1.24 (1.12-1.38) ***
Mental health	2.02 (1.89-2.15) ***	1.62 (1.51-1.73) ***	1.75 (1.54-1.97) ***	1.40 (1.22-1.58) ***
Painful conditions	1.62 (1.55-1.70) ***	1.41 (1.34-1.48) ***	1.40 (1.28-1.52) ***	1.24 (1.13-1.35) **

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
 Model 1: Adjusted for age, sex and socioeconomic status
 Model 2: Adjusted for age, sex, socioeconomic status, smoking, alcohol frequency, body mass index and physical activity

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Outcome	Self-report COPD compared with no COPD N=502,640		GOLD COPD compared with no COPD N=496,943	
	Model 1 N=502,013	Model 2 N=487,718	Model 1 N=496,324	Model 2 N=482,378
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Multimorbidity (≥4 conditions)	3.49 (3.28-3.70) ***	2.79 (2.61-2.98) ***	2.34 (2.10-2.63) ***	1.99 (1.75-2.25) ***
Polypharmacy (≥5 medications)	3.85 (3.68-4.03) ***	3.30 (3.15-3.46) ***	3.47 (3.20-3.75) ***	3.20 (2.95-3.48) ***
Polypharmacy (≥10 medications)	5.72 (5.36-6.10) ***	4.42 (4.11-4.75) ***	4.20 (3.72-4.73) ***	3.56 (3.12-4.05) ***

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
 Model 1: Adjusted for age, sex and socioeconomic status
 Model 2: Adjusted for age, sex, socioeconomic status, smoking, alcohol frequency, body mass index and physical activity

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ADR	Self-report COPD compared with no COPD N=502,640		GOLD COPD compared with no COPD N=496,943	
	Model 1 N=502,013	Model 2 N=487,718	Model 1 N=496,943	Model 2 N=482,378
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Falls	2.27 (2.13 – 2.42) ***	1.83 (1.71-1.96) ***	1.66 (1.47 – 1.87) ***	1.49 (1.30-1.69) ***
Constipation	2.71 (2.54 – 2.89) ***	2.66 (2.39-2.96) ***	2.18 (1.77 – 2.64) ***	1.82 (1.47-2.24) ***
Urinary retention	3.38 (2.94 – 3.87) ***	2.59 (2.22-3.0) ***	1.98 (1.44 – 2.64) ***	1.64 (1.18-2.21) **
CNS Depression	3.75 (3.31 – 4.25) ***	2.81 (2.45-3.22) ***	2.29 (1.73 – 2.95) ***	1.87 (1.40-2.43) ***
Bleeding	4.60 (3.35 – 6.19) ***	3.39 (2.40-4.66) ***	2.63 (1.25 – 4.80) **	1.76 (0.75-3.48) §
Renal injury	2.22 (1.86 – 2.62) ***	1.84 (1.53-2.19) ***	1.94 (1.41 – 2.58) ***	1.84 (1.33-2.49) ***

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
 Model 1: Adjusted for age, sex and socioeconomic status
 Model 2: Adjusted for age, sex, socioeconomic status, smoking, alcohol frequency, body mass index and physical activity

Subgroup analyses – comparing COPD with no COPD among participants with specific categories of comorbidity

Table S4. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with cardiovascular disease (CVD)

ADR	Self-report COPD plus CVD compared with CVD alone (no COPD) N=156,848	GOLD COPD plus CVD compared with CVD alone (no COPD) N=154,047
	Model 1 N=156,667	Model 1 N=153,852
	OR (95% CI)	OR (95% CI)
Falls	1.92 (1.79-2.07) ***	1.59 (1.39-1.82) ***
Constipation	2.89 (2.58-3.23) ***	2.06 (1.63-2.57) ***
Urinary retention	2.78 (2.33-3.28) ***	1.92 (1.30-2.72) ***
CNS Depression	3.17 (2.71-3.69) ***	2.17 (1.54-2.97) ***
Bleeding	4.00 (2.85-5.48) ***	2.26 (0.96-4.44) *
Renal injury	1.90 (1.59-2.25) ***	1.82 (1.31-2.45) ***

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
Model 1: Adjusted for age, sex and socioeconomic status

Table S5. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with cancer

ADR	Self-report COPD plus cancer compared with cancer alone (no COPD) N=38,623	GOLD COPD plus cancer compared with cancer alone (no COPD) N=37,958
	Model 1 N=38,575	Model 1 N= 37,912
	OR (95% CI)	OR (95% CI)
Falls	2.35 (1.95-2.81) ***	1.49 (1.00-2.13) *
Constipation	3.55 (2.73-4.56) ***	2.21 (1.22-3.68) **
Urinary retention	3.65 (2.52-5.13) ***	1.99 (0.78-4.14) §
CNS Depression	3.74 (2.66-5.14) ***	2.04 (0.86-4.04) §
Bleeding	4.69 (1.91-9.86) ***	2.20 (0.12-10.23) §
Renal injury	2.0 (1.17-3.20) **	2.26 (0.89-4.71) §

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
Model 1: Adjusted for age, sex and socioeconomic status

Table S6. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with gastrointestinal disease (GI)

ADR	Self-report COPD plus GI compared with GI alone (no COPD) N=58372	GOLD COPD plus GI compared with GI alone (no COPD) N=57103
	Model 1 N=58,299	Model 1 N=57,031
	OR (95% CI)	OR (95% CI)
Falls	2.18 (1.92-2.46) ***	1.46 (1.13-1.87) **
Constipation	2.70 (2.29-3.16) ***	1.58 (1.08-2.24) *
Urinary retention	2.64 (2.12-3.26) ***	1.46 (0.83-2.37) §
CNS Depression	3.02 (2.47-3.66) ***	1.50 (0.88-2.37) §
Bleeding	3.88 (2.27-6.25) ***	3.18 (0.97-7.63) §
Renal injury	1.99 (1.37-2.80) ***	1.22 (0.48-2.51) §

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
Model 1: Adjusted for age, sex and socioeconomic status

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Table S7. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with mental health conditions (MH)		
ADR	Self-report COPD plus MH compared with MH alone (no COPD) N=36,949	GOLD COPD plus MH compared with MH alone (no COPD) N=36126
	Model 1 N=36,885	Model 1 N=36,065
	OR (95% CI)	OR (95% CI)
Falls	2.21 (1.90-2.56) ***	1.35 (0.99-1.82) §
Constipation	2.33 (1.93-2.81) ***	1.62 (1.08-2.34) *
Urinary retention	2.17 (1.71-2.74) ***	1.42 (0.82-2.29) §
CNS Depression	2.53 (2.04-3.12) ***	1.66 (1.03-2.54) *
Bleeding	2.86 (1.77-4.17) ***	1.94 (0.76-4.05) §
Renal injury	1.86 (1.19-2.79) **	1.27 (0.45-2.80) §
§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001 Model 1: Adjusted for age, sex and socioeconomic status		

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Table S8. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with painful conditions		
ADR	Self-report COPD plus painful conditions compared with painful conditions alone (no COPD) N=83,992	GOLD COPD plus painful conditions compared with painful conditions alone (no COPD) N=82,388
	Model 1 N=83,895	Model 1 N=82,294
	OR (95% CI)	OR (95% CI)
Falls	1.99 (1.79-2.19) ***	1.45 (1.19-1.75) ***
Constipation	2.54 (2.21-2.91) ***	1.50 (1.10-2.00) **
Urinary retention	2.46 (2.03-2.96) ***	1.11 (0.64-1.75) §
CNS Depression	2.71 (2.28-3.21) ***	1.40 (0.90-2.06) §
Bleeding	3.50 (2.37-5.01) ***	2.20 (0.86-4.54) §
Renal injury	1.66 (1.30-2.09) ***	1.49 (0.93-2.25) §
§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001 Model 1: Adjusted for age, sex and socioeconomic status		

Appendix 4: Specific medications in UK Biobank participants with and without COPD						
Medications	Control n=494323 count (%)	Self-report COPD n=8317 count (%)	GOLD COPD			
			All n=2620 count (%)	Mild n=399 count (%)	Moderate n=1409 count (%)	Severe n= 812 count (%)
Total number of medications						
≥1	356406 (72.1)	7670 (92.2)	2452 (93.6)	352 (88.2)	1321 (93.8)	779 (95.9)
≥5	87286 (17.7)	4312 (51.8)	1349 (51.5)	171 (42.9)	702 (49.8)	476 (58.6)
≥10	10678 (2.2)	1269 (15.3)	329 (12.6)	31 (7.8)	172 (12.2)	126 (15.5)
Respiratory						
Short acting B ₂ agon.	22615 (4.6)	3328 (40.0)	1245 (47.5)	123 (30.8)	614 (43.6)	508 (62.6)
LABA	9819 (2.0)	2357 (28.3)	905 (34.5)	93 (23.3)	411 (29.2)	401 (49.3)
LAMA	597 (0.1)	1345 (16.2)	581 (22.2)	33 (8.3)	265 (18.8)	283 (34.9)
ICS	15309 (3.1)	2638 (31.7)	962 (36.7)	98 (24.6)	471 (33.4)	393 (48.4)
LABA+ICS	7259 (1.5)	1842 (22.1)	699 (26.7)	67 (16.8)	313 (22.2)	319 (39.3)
Prednisolone	3127 (0.6)	280 (3.4)	82 (3.1)	12 (3.0)	27 (1.9)	43 (5.3)
Mucolytic	174 (0.04)	187 (2.2)	49 (1.9)	1 (0.3)	10 (0.7)	38 (4.7)
Cardiovascular						
Antiplatelet	21817 (4.4)	894 (10.7)	268 (10.2)	31 (7.8)	158 (11.2)	79 (9.7)
ACE-inhibitor	44991 (9.1)	1276 (15.3)	367 (14.0)	33 (8.3)	198 (14.1)	136 (16.7)
ARB	17911 (3.6)	565 (6.8)	159 (6.1)	17 (4.3)	83 (5.9)	59 (7.2)
Calcium CB	14317 (2.9)	627 (7.5)	196 (7.5)	23 (5.8)	106 (7.5)	67 (8.3)
Statin	73439 (14.9)	2278 (27.4)	707 (27.0)	72 (18.0)	395 (28.0)	240 (29.6)
GTN	4425 (0.9)	373 (4.5)	110 (4.2)	8 (2.0)	70 (5.0)	32 (3.9)
ISMN	2814 (0.6)	244 (2.9)	68 (2.6)	5 (1.3)	42 (3.0)	21 (2.6)
Loop diuretic	4836 (1.0)	415 (5.0)	107 (4.1)	10 (2.5)	51 (3.6)	46 (5.7)
Thiazide	21961 (4.4)	637 (7.7)	196 (7.5)	22 (5.5)	108 (7.7)	66 (8.1)
Warfarin	4934 (1.0)	238 (2.9)	67 (2.6)	6 (1.5)	33 (2.3)	28 (3.4)
Diabetes						
Insulin	4643 (0.9)	161 (1.9)	35 (1.3)	2 (0.5)	23 (1.6)	3 (0.4)
Metformin	13754 (2.8)	448 (5.4)	102 (3.9)	7 (1.8)	57 (4.0)	38 (4.7)
Sulphonylurea	4901 (1.0)	158 (1.9)	35 (1.3)	2 (0.5)	17 (1.2)	16 (2.0)
Thiazolidindione	2212 (0.4)	60 (0.7)	17 (0.6)	1 (0.3)	10 (0.7)	6 (0.7)
Gastrointestinal						
PPI	42012 (8.5)	1989 (23.9)	522 (19.9)	79 (19.8)	286 (20.3)	157 (19.3)
Antacid	2435 (0.5)	146 (1.8)	25 (1.0)	7 (1.8)	10 (0.7)	8 (1.0)
H ₂ RA.	7772 (1.6)	325 (3.9)	89 (3.4)	15 (3.8)	53 (3.8)	21 (2.6)
Laxative	5787 (1.8)	317 (3.8)	81 (3.1)	11 (2.8)	40 (2.8)	30 (3.7)
Pain						
Paracetamol	82376 (16.7)	2752 (33.1)	790 (30.2)	111 (27.8)	446 (31.6)	233 (28.7)
NSAID	45909 (9.3)	1149 (13.8)	319 (12.2)	50 (12.5)	175 (12.4)	94 (11.6)
Weak opiate	18736 (3.8)	1209 (14.5)	336 (12.8)	48 (12.0)	191 (13.6)	97 (11.9)
Strong opiate	1071 (0.2)	106 (1.8)	32 (1.2)	5 (1.3)	16 (1.1)	11 (1.4)
Mental health						
SSRI+related	15394 (3.1)	747 (9.0)	175 (6.7)	31 (7.8)	100 (7.1)	44 (5.4)
Tricyclic	4229 (0.9)	206 (2.5)	49 (1.9)	11 (2.8)	25 (1.8)	13 (1.6)
Antipsychotic	2237 (0.5)	107 (1.3)	30 (1.1)	5 (1.3)	16 (1.1)	9 (1.1)
Benzodiazepine	2316 (0.5)	182 (2.2)	47 (1.8)	6 (1.5)	28 (2.0)	13 (1.6)
Metabolic						
Thyroxine	20980 (4.2)	560 (6.7)	150 (5.7)	27 (6.8)	92 (6.5)	31 (3.8)
Bisphosphonate	3655 (0.7)	189 (2.3)	66 (2.5)	15 (3.8)	32 (2.3)	19 (2.3)

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	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6,9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
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	6-8
Bias	9	Describe any efforts to address potential sources of bias	14,15
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7,8,9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8-10
		(b) Describe any methods used to examine subgroups and interactions	9,10
		(c) Explain how missing data were addressed	10
		(d) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	9,10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11, figure 1
		(b) Give reasons for non-participation at each stage	11, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	11-13, figure 2, appendix 3
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	11-13, figure 2, appendix 3
		(b) Report category boundaries when continuous variables were categorized	12,13
		(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	12,13, Appendix 3,
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	14,15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15,16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15,16,17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17,18

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

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

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Examining Patterns of Multimorbidity, Polypharmacy and Risk of Adverse Drug Reactions in Chronic Obstructive Pulmonary Disease: A Cross-Sectional UK Biobank Study

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3 **Examining Patterns of Multimorbidity, Polypharmacy and Risk of Adverse Drug Reactions in**
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5 **Chronic Obstructive Pulmonary Disease: A Cross-Sectional UK Biobank Study**
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Abstract

Objective: This study aims: (1) to describe the pattern and extent of multimorbidity and polypharmacy in UK Biobank participants with chronic obstructive pulmonary disease (COPD); and (2) to identify which comorbidities are associated with increased risk of adverse drug reactions (ADRs) resulting from polypharmacy.

Design: Cross-sectional.

Setting: Community cohort.

Participants: UK Biobank participants comparing self-reported COPD (n=8317) with no COPD (n=494,323).

Outcomes: Multimorbidity (\geq four conditions) and polypharmacy (\geq five medications) in participants with COPD versus those without. Risk of ADRs (taking \geq three medications associated with falls, constipation, urinary retention, central nervous system (CNS) depression, bleeding or renal injury) in relation to the presence of COPD and individual comorbidities.

Results: Multimorbidity was more common in participants with COPD than those without (17% vs. 4%). Polypharmacy was highly prevalent (52% with COPD taking \geq five medications vs 18% in those without COPD). Adjusting for age, sex and socioeconomic status, those with COPD were significantly more likely than those without to be prescribed \geq 3 medications contributing to falls (Odds ratio (OR) 2.27, 95% confidence interval (CI) 2.13 to 2.42), constipation (OR 3.42, 95% CI 3.10 to 3.77), urinary retention (OR 3.38, 95% CI 2.94 to 3.87), CNS depression (OR: 3.75, 95% CI 3.31 to 4.25), bleeding (OR 4.61, 95% CI 3.35 to 6.19) and renal injury (OR 2.22, 95% CI 1.86 to 2.62). Concomitant cardiovascular disease was associated with the greatest risk of taking \geq 3 medications associated with falls/renal injury. Concomitant mental health conditions were most strongly associated with medications linked with CNS depression/urinary retention/bleeding.

Conclusions: Multimorbidity is common in COPD and associated with high levels of polypharmacy. Co-prescription of drugs with various ADRs is common. Future research should examine the effects

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3 on healthcare outcomes of co-prescribing multiple drugs with similar potential ADRs. Clinical
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5 guidelines should emphasise assessment of multimorbidity and ADR risk.
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22 **Strengths and Limitations**

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- 25 • This paper assesses multimorbidity, polypharmacy and risk of adverse drug reactions in UK
26 Biobank participants with self-reported COPD compared with those without COPD.
- 27 • Baseline variables from the UK Biobank assessment centre were used to adjust for potential
28 confounders.
- 29 • Cumulative risk of common adverse drug reactions was quantified by identifying UK Biobank
30 participants taking three or more medications associated with similar adverse drug
31 reactions.
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- 33 • Analyses were repeated using a subgroup of participants with spirometry data confirming
34 airflow obstruction.
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- 36 • Medication and comorbidity data rely on participant self-report, and may thus be
37 susceptible to bias or inaccuracy.
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BACKGROUND

In people with Chronic Obstructive Pulmonary Disease (COPD), multimorbidity (the presence of two or more long-term conditions (LTCs)) is highly prevalent.(1-4) A recent meta-analysis of 29 datasets demonstrated that those with COPD are significantly more likely to be diagnosed with a range of cardiovascular comorbidities than those without COPD (we will use the term comorbidity when referring to specific conditions in addition to COPD, and multimorbidity to refer to the presence of two or more LTCs).(5) Other LTCs with known increased prevalence in COPD include obesity,(6) depression,(7-10) gastro-oesophageal reflux disease,(11-13) osteoporosis,(14-16) and lung cancer.(17, 18) Each of these conditions has been associated with poorer health related outcomes in COPD when compared to those with no comorbidity.(19-30) The overall burden of multimorbidity also impacts prognosis in COPD, for example higher number of comorbidities is associated with higher risk of mortality,(31) and higher burden of morbidity assessed using the Charlson index and the COPD-specific comorbidity test (COTE) is associated with higher risk of all-cause and respiratory specific mortality.(32, 33) The importance of considering the impact of multimorbidity in the management of long-term conditions is increasingly recognised, particularly in the context of an ageing society in which the prevalence of multimorbidity is growing.(34) However, an immature evidence base means that disease specific guidelines often lack specific recommendations with respect to multimorbidity.(35) The prevalence and prognostic significance of multimorbidity in COPD make it a potentially useful exemplar condition in which to consider the specific implications of different patterns of multimorbidity. Polypharmacy is one such implication.

Multimorbidity in the general population is associated with polypharmacy (often defined as concomitant use of ≥ 5 or ≥ 10 pharmacological agents).(36) Polypharmacy has been associated with increased risk of adverse drug reactions (ADRs)(37-39) and potentially preventable hospital admissions, particularly in the elderly.(40, 41) This is particularly pertinent in an ageing society, in

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3 which the a rising prevalence of polypharmacy has been observed.(34, 37) It has been demonstrated
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5 that diagnosis of COPD is associated with increased risk of polypharmacy.(42, 43) This is, in large
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7 measure, due to the high burden of extra-pulmonary comorbidities.(44) However, little is known
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9 about the risk of ADRs in the context of multimorbidity in COPD.
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15 Given the well-established burden of multimorbidity and polypharmacy in COPD, it is likely that
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17 those with COPD are at increased risk of ADRs resulting from polypharmacy. Previous analyses have
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19 not focused on the risk of specific ADRs, or assessed which LTCs increase this risk, instead reporting
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21 overall counts of prescribed medication. Data collected for the UK Biobank cohort offers an
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23 opportunity to assess how multimorbidity in COPD relates to polypharmacy and to assess the
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25 prevalence of co-prescription of medications with similar ADRs.
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31 This paper aims:

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34 • To describe the pattern and extent of multimorbidity and polypharmacy in UK Biobank
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36 participants with COPD.
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38 • To identify which LTCs in people with COPD are associated with increased risk of ADRs
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40 resulting from polypharmacy.
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METHODS

Data collection

The UK Biobank is a large, population cohort that recruited voluntary participants from throughout the United Kingdom. Between 2006 and 2010, UK Biobank recruited 502,640 participants aged 37 to 73. Participants underwent baseline assessments at one of 22 assessment centres throughout England, Scotland and Wales. Sociodemographic and lifestyle details were recorded using touchscreen questionnaires. Townsend scores were derived from participant postcodes to provide an area-based measure of socioeconomic deprivation. Self-reported LTCs, prescribed and over-the-counter medications, smoking status (current, previous or never) and frequency of alcohol intake (never / special occasions only, one-three times a month, at least once a week) were recorded from a touchscreen questionnaire and subsequent verbal interview with a study nurse. Physical activity was self-reported based on a questionnaire administered in the UK Biobank assessment centre.⁽⁴⁵⁾ We classified the responses into: none (no physical activity in the last four weeks), low (light 'DIY' activity only in the last four weeks), medium (heavy DIY and/or walking for pleasure and/or other exercises in the last four weeks), and high (strenuous sports in the last four weeks).

Study centre staff also collected physical measures including height and weight (to calculate body mass index (BMI)) and spirometry. Spirometry was performed using a Vitalograph Pneumotrac 6800. Individual reasons for contraindications to attempting spirometry were not recorded but, according to protocol, these included chest infection in the last month, history of collapsed lung, and heart attack or surgery in the past three months. Full details of the Biobank spirometry protocol are available at <https://biobank.ctsu.ox.ac.uk/crystal/docs/Spirometry.pdf>. In brief, participants were allowed up to three attempts to provide two reproducible spirometry measurements. Where the reproducibility of the first two was deemed acceptable (<5% variation in both FEV1 and FVC) a third measurement was not performed. All values were recorded along with any error messages generated. As per the American Thoracic Society/European Respiratory Society (ATS/ERS) end-of-

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3 test criteria, we interpreted as valid any measurement with no error message or if 'user accepted'
4 was specified.(46) No post-bronchodilator measurements were recorded, which deviates from the
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test criteria, we interpreted as valid any measurement with no error message or if 'user accepted' was specified.(46) No post-bronchodilator measurements were recorded, which deviates from the ATS/ERS guidelines and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for COPD.(47, 48)

Participants provided full informed consent to participate in UK Biobank and this study had full ethical approval from the NHS National Research Ethics Service for UK Biobank studies (Ref 16/NW/0274); this study is part of UK Biobank approved project number 14151.

Defining COPD

Participants reporting to have been diagnosed with chronic obstructive pulmonary disease, chronic bronchitis, or emphysema at the nurse-led interview were coded as having 'self-reported COPD'.

Due to the potential inaccuracies of using self-reported diagnoses, we identified a subset of those with self-reported COPD who met an adaptation of the Global Initiative for Obstructive Lung Disease (GOLD) spirometry criteria for COPD.(48) This subset, referred to as 'GOLD COPD', was used as a sensitivity analysis for self-reported COPD, and to stratify findings by severity of airflow obstruction. For participants with self-report COPD and valid spirometry measurements, we calculated the ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) using the highest measurement for each participant meeting the American Thoracic Society/European Respiratory Society end-of-test criteria.(46) Those with a FEV1/FVC ratio <0.7 were classed as having an obstructive deficit and thus meeting the GOLD diagnostic criteria for COPD. We used the Hankinson equation,(49) based on recorded age, sex and height, to calculate predicted FEV1 values for each participant. Those with GOLD COPD were classified on the basis of their best available FEV1 measurement as having mild ($>80\%$ predicted FEV1), moderate (50-80% predicted FEV1), or severe ($<50\%$ predicted FEV1) airflow obstruction in line with the GOLD COPD guidelines.(48)

Defining long term conditions and medications

All LTCs were defined by self-report. The list of included LTCs was taken from a list of 42 morbidities originally established for a large multimorbidity epidemiological study in Scotland, through systematic review, the Quality and Outcomes Framework, NHS Scotland and an expert panel (34), and subsequently amended for UK Biobank (50). The inclusion of 'other painful conditions' comprised LTCs in which pain is a predominant feature (particularly as this is likely to influence medication use). It should be noted that such a list is not exhaustive, but intended to cover common conditions frequently requiring prescription of analgesics (e.g. osteoarthritis, back pain, headaches etc.). Morbidities were categorised for the purposes of this analysis into cardiovascular disease, gastrointestinal disease, mental health conditions, cancer, and painful conditions/inflammatory arthropathies (comprising the list of 'other painful conditions' mentioned above, plus connective tissue diseases). Full details of conditions comprising each category can be found in appendix 1.

Medication data were collected by self-report. Medications were coded by mechanism of action according to the British National Formulary (BNF) (e.g. Angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, etc.).(51) For some situations where more than one medication with a similar mechanism of action may be commonly co-prescribed (e.g. aspirin and clopidogrel, both antiplatelets) these were coded separately. A complete list of the medications coded within each class can be found in appendix 2.

We defined those at risk of specific ADRs as anyone on 3 or more medications with similar potential ADRs, based on information provided in the *Scottish Government Model of Care Polypharmacy Working Group: Polypharmacy Guidance*.(52) This guideline cross-tabulates commonly prescribed medications with common ADRs to help identify those at cumulative risk of ADRs. This document groups common medications by similar potential ADRs. While this list is not all-inclusive, and the cut-

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3 off value of three or more medications is arbitrary, this does allow an estimation of the cumulative
4 risk of specific ADRs. We identified six potential ADRs (falls/fractures, constipation, urinary
5 retention, CNS depression, bleeding and renal injury) for which the proportion of participants taking
6 three or more associated medications could be assessed. It should be noted that several of these
7 event (e.g. falls/fractures, CNS depression) are often multifactorial, and medication may be a
8 contributing factor rather than a definitive cause. As the guideline acknowledges, however, these
9 are clinical events of which the risk is increased by taking multiple associated medications.
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21 **Statistical analysis**

22 All analyses were planned prior to inspection of the data.
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26 **Baseline variables**

27 Comparisons were made between participants with self-reported COPD and the rest of the cohort
28 (who did not report COPD). Age, sex, smoking status, deprivation (Townsend score), BMI, physical
29 activity and frequency of alcohol intake were compared using χ^2 test for categorical variables, χ^2 test
30 for trend for ordinal variables, and Mann-Whitney-U test for continuous variables. Total number of
31 morbidities, prevalence of specific morbidities, number of self-reported prescribed medications, and
32 proportion of participants taking each class of medication (Appendix 2), were also compared
33 between those with self-reported COPD and the rest of the cohort. All comparisons were repeated
34 comparing participants with GOLD COPD only with those without COPD, stratifying by severity of
35 airflow obstruction.
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49 **Multimorbidity and polypharmacy**

50 Logistic regression analyses were used to compare participants with self-reported COPD and those
51 without COPD. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for:
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- the presence of cardiovascular disease, cancer, gastrointestinal disease, mental health conditions and painful conditions/inflammatory arthropathies
- the presence of four or more morbidities (excluding COPD)
- the use of five or more, and 10 or more, medications (two separate models)

Models were initially adjusted for age, sex and socioeconomic deprivation (model 1), then adjusted for the addition of smoking status, alcohol frequency, BMI and physical activity (model 2). These analyses were repeated comparing those with GOLD COPD only to those without COPD.

Risk of ADRs

For each potential ADR (falls/fractures, constipation, urinary retention, CNS depression, bleeding and renal injury) participants taking three or more medications associated with that ADR were identified. The following comparisons were then made:

- Unadjusted percentages at risk of each ADR were calculated for participants without COPD, with self-reported COPD, and with self-reported COPD plus each category of LTC (cardiovascular disease, cancer, gastrointestinal disease, mental health conditions and painful conditions/inflammatory arthropathies) to give an impression of the ADR risk in COPD, and identify LTCs in those with COPD that may increase this risk.
- ORs of being at risk of each ADR were calculated comparing those with self-reported COPD to those without COPD adjusting for age, sex and socioeconomic deprivation (model 1) and for age, sex, socioeconomic deprivation, smoking status, alcohol frequency, BMI and physical activity (model 2).
- ORs of being at risk of each ADR were calculated comparing those with and without self-reported COPD in each LTC category to (i.e. participants with cardiovascular disease alone compared to participants with cardiovascular disease plus COPD, etc.). This was intended to identify whether specific patterns of multimorbidity in COPD are associated with increased

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3 ADR risk. Adjustment for a wide range of potential confounders was not appropriate in
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5 these models due to the smaller number of participants in each model.
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8 Each analysis was repeated comparing GOLD COPD only to those without COPD. Less than 3% of
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10 participants (with or without COPD) had missing data for potential confounding variables (table 1).
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12 Those with missing data were excluded from adjusted analyses. Spirometry data were missing for
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14 3591 participants with self-report COPD (43%), hence the use of the GOLD COPD subset as a
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16 sensitivity analysis.
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19 All analyses were performed using R statistical software (version 3.3.1).
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RESULTS

At the time of recruitment, 8317 out of 502,619 participants reported having COPD (1.7%) and are referred to here as the self-report COPD group. Of those who self-reported COPD, 4726 (57%) had valid spirometry measurements. Spirometry was contraindicated or not available in 2507 of those with self-reported COPD. Spirometry measurements did not meet the ATS/ESR end-of-test criteria in 1084 participants.⁽⁴⁶⁾ Of those with valid spirometry, 2620 (55%) met the GOLD criteria for airflow obstruction (399 (15%) mild, 1409 (54%) moderate, 812 (31%) severe, see Figure 1) and are referred to here as GOLD COPD.

Baseline variables

Table 1 describes and compares the characteristics of those with and without COPD in UK Biobank. Participants with COPD (both self-report and GOLD) were significantly older, more socioeconomically deprived, and less physically active. A higher proportion of those with COPD were male, obese and had a history of smoking.

Table 1. Baseline variables								
Characteristic	No COPD n=494323		COPD (self-report) n=8317			GOLD GOPD n=2620		
	Count	%	Count	%	p-value	Count	%	p-value
Sex								
Male	224906	45.5	4268	51.3		1426	54.4	
Female	269417	54.5	4049	48.7	<0.001	1194	45.6	<0.001
Age	Median: 58 IQR: 50-63		Median: 62 IQR: 57-66		<0.001	Median: 63 IQR: 59-66		<0.001
Ethnicity								
White	464770	94.5	8052	97.3		2620	100	
Other	26821	5.4	219	2.6	<0.001	0	0	<0.001
Missing	2732		46			0	0	
Socioeconomic deprivation quintile								
1 (least deprived)	99672	20.2	1015	12.2		309	11.8	
2	98977	20.0	1142	13.7		362	13.8	
3	99013	20.1	1399	16.8		440	16.8	
4	98660	20.0	1735	20.9		580	22.2	
5 (most deprived)	98385	19.7	3015	36.3	<0.001	926	35.4	<0.001
Missing	616		11			3		
Smoking status								
Current	50817	10.3	2172	26.3		833	32.2	
Previous	169015	34.4	4083	49.5		1398	54.0	
Never	271602	55.3	1999	24.2	<0.001	360	13.9	<0.001
Missing	2889		63			29		
Alcohol frequency								
Daily	100070	20.3	1720	20.7		618	23.6	
3-4 times/week	114058	23.1	1404	16.9		475	18.2	
1-2 times/week	127459	25.9	1863	22.5		561	21.5	
1-3 times/month	54979	11.2	894	10.8		289	11.1	
Occasional	56707	11.5	1322	15.9		387	14.8	<0.001
Never	39569	8.0	1092	13.2	<0.001	284	10.9	
Missing	1481		22			6		
BMI								
<18.5	2478	0.5	148	1.8		56	2.2	
18.5-24.9	155282	31.8	2185	26.8		829	31.9	
25.0-29.9	211102	43.2	3165	38.9		1049	40.4	
>30	119813	24.5	2647	32.5	<0.001	665	25.6	<0.001
Missing	5648		172			21		
Physical activity								
High	49827	10.6	250	3.1		70	2.7	
Medium	387766	79.6	5838	72.0		1902	73.3	
Low	18354	3.8	589	7.3		203	7.8	
None	31425	6.4	1433	17.7	<0.001	421	16.2	<0.001
Missing	6951		207			24		
FEV1 (% predicted)								
>80	272109	78.0	1853	39.2		399	15.2	
50-79	71727	20.6	2022	42.8		1409	53.8	
<50	4841	1.4	851	18.0	<0.001	812	31.0	<0.001
Missing	145646		3591			1061		

Multimorbidity and polypharmacy

Prevalence of each category of comorbidity was higher in those with COPD than without (table 2).

After controlling for age, sex and socioeconomic status, those with self-reported COPD were significantly more likely than those without to have each category of LTC examined: cardiovascular disease (OR 1.45; 95% confidence interval (CI) 1.39 to 1.52) , cancer (1.29; 1.2 to 1.39), gastrointestinal disease (1.76; 1.67 to 1.86) , mental health conditions (2.02; 1.89 to 2.15) , and painful conditions (1.54; 1.46 to 1.62). Results for GOLD COPD also suggested higher likelihood of each LTC compared to those without COPD, although the ORs were lower and results for cancer not statistically significant (appendix 3). Results were similar after adjusting for additional confounders (smoking status, alcohol frequency, BMI and physical activity) with the exception of cardiovascular disease in GOLD COPD, which was no longer significantly associated (1.08; 0.99 to 1.18) (appendix 3).

Table 2: Long Term Conditions in those with and without COPD						
	Control n=494323 count (%)	Self-report COPD n=8317 count (%)	GOLD COPD			
			All n=2620 count (%)	Mild n=399 count (%)	Moderate n=1409 count (%)	Severe n= 812 count (%)
Total comorbidities (excluding COPD) ≥4	19959 (4.0)	1389 (16.7)**	331 (12.6)**	46 (11.5)	191 (13.5)	94 (11.6)
Total number of medications						
≥1	356406 (72.1)	7670 (92.2)**	2452 (93.6)**	352 (88.2)	1321 (93.8)	779 (95.9)
≥5	87286 (17.7)	4312 (51.8)**	1349 (51.5)**	171 (42.9)	702 (49.8)	476 (58.6)
≥10	10678 (2.2)	1269 (15.3)**	329 (12.6)**	31 (7.8)	172 (12.2)	126 (15.5)
Prevalence of comorbidities						
Cardiovascular	152891 (30.9)	3957 (47.6)**	1156 (44.1)**	142 (35.6)	611 (43.4)	403 (49.6)
Hypertension	130119 (26.3)	3206 (38.5)**	916 (35.0)**	112 (28.1)	483 (34.3)	321 (39.5)
CHD	21560 (4.4)	1171 (14.1)**	315 (12.0)**	31 (7.6)	185 (13.1)	99 (12.2)
Diabetes	24737 (5.0)	766 (9.1)**	189 (7.2)**	16 (4.0)	109 (7.7)	64 (7.9)
Stroke/TIA	8459 (1.7)	395 (4.7)**	98 (3.7)**	11 (2.8)	51 (3.6)	36 (4.4)
AF	3552 (0.7)	99 (1.2)**	34 (1.3)**	3 (0.8)	16 (1.1)	15 (1.8)
Heart failure	768 (0.2)	35 (0.4)**	6 (0.2)	0	1 (0.1)	5 (0.6)
Respiratory						
Asthma	55245 (11.2)	3048 (36.6)**	984 (37.6)**	142 (35)	523 (37.1)	319 (39.3)
Pulmonary embolus	4354 (0.9)	264 (3.2)**	65 (2.5)**	12 (3.0)	32 (2.2)	21 (2.5)
Bronchiectasis	968 (0.2)	167 (2.0)**	39 (1.5)**	7 (1.8)	17 (1.2)	15 (1.8)
Pulmonary fib.	504 (0.1)	67 (0.8)**	18 (0.7)**	3 (0.8)	12 (0.9)	3 (0.4)
Cancer	37686 (7.6)	937 (11.3)	272 (10.4)	47 (11.8)	146 (10.4)	79 (9.7)
Lung	405 (0.1)	52 (0.6)**	15 (0.6)**	0	7 (0.5)	8 (1.0)
Breast	11311 (2.3)	210 (2.5)*	57 (2.2)	12 (3.0)	30 (2.1)	15 (1.8)
Prostate	3588 (0.7)	105 (1.3)**	30 (1.1)*	5 (1.3)	12 (0.9)	13 (1.6)
GI	2925 (0.6)	96 (1.2)**	34 (1.3)**	6 (1.5)	19 (1.3)	9 (1.1)
Haem	6170 (1.2)	124 (1.5)*	34 (1.3)	5 (1.3)	17 (1.2)	12 (1.5)
Gastrointestinal	55635 (11.5)	1737 (20.9)**	468 (17.9)**	76 (19.0)	254 (18.0)	138 (17.0)
Dyspepsia	37819 (7.7)	1257 (15.1)**	348 (13.3)**	53 (13.3)	189 (13.4)	106 (13.1)
Diverticular dis	5181 (1.0)	224 (2.7)**	54 (2.1)**	6 (1.5)	32 (2.3)	16 (2.0)
IBS	11203 (2.3)	291 (3.5)**	64 (2.4)**	17 (4.3)	35 (2.5)	12 (1.5)
CLD	935 (0.2)	36 (0.4)**	10 (0.4)*	2 (0.5)	10 (0.7)	3 (0.4)
Mental Health	35822 (7.2)	1127 (13.6)**	304 (11.6)**	54 (13.5)	162 (11.5)	88 (10.8)
Depression	27578 (5.6)	901 (10.8)**	233 (8.9)**	42 (10.5)	128 (9.1)	63 (7.8)
Anxiety	8781 (1.8)	245 (2.9)**	69 (2.6)**	13 (3.3)	36 (2.6)	20 (2.5)
Schizophrenia/ bipolar	1918 (0.4)	79 (0.9)**	27 (1.0)**	3 (0.7)	15 (1.1)	9 (1.1)
Other						
Other painful	81733 (16.5)	2259 (27.2)**	655 (25.0)**	115 (28.8)	367 (26.0)	173 (21.3)
Osteoporosis	7700 (1.6)	342 (4.1)**	128 (4.9)**	21 (5.3)	67 (4.8)	40 (4.9)
Connective tissue disease	10642 (2.2)	391 (4.7)**	112 (4.3)**	19 (4.8)	72 (5.1)	21 (2.6)

Compared with control (χ^2): * : p<0.05, ** : p<0.001

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3 Morbidity counts (excluding COPD) and counts of prescribed medication are shown in table 2
4
5 comparing those with COPD, stratified by severity of airflow obstruction, with those without. Those
6
7 with COPD had higher numbers of LTCs and more prescribed medications than those without. There
8
9 was a trend towards more prescribed medications in those with greater severity of airway
10
11 obstruction. After controlling for age, sex and socioeconomic status, those with self- report COPD
12
13 were more likely to report ≥ 4 LTCs (3.49; 3.28 to 3.71), ≥ 5 medications (3.85; 3.68 to 4.03), and ≥ 10
14
15 medications (5.72; 5.36 to 6.10) than those without COPD. Results were similar for GOLD COPD and
16
17 remained statistically significant after adjusting for smoking status, alcohol frequency, BMI and
18
19 physical activity (appendix 3).
20

21 22 **ADR Risk**

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24
25 Counts and percentages of participants taking specific medications are shown in appendix 4.
26
27 Participants with COPD (self-report and GOLD) were more likely than those without COPD to be
28
29 prescribed drugs across a range of disease areas, reflecting the range of LTCs present among those
30
31 with COPD. The percentages of participants within each category (no COPD, COPD, and COPD with
32
33 specific LTCs) taking three or more medications associated with a similar ADR is shown in Figure 2.
34
35 For each category of ADR a higher proportion of participants with COPD reported taking three or
36
37 more associated medications than those without COPD. This increased further with multimorbidity.
38
39 Participants with COPD plus cardiovascular disease had the highest percentage taking three or more
40
41 medications with a risk of falls or renal injury. Participants with COPD plus mental health conditions
42
43 had the highest percentages taking three or more medications with a risk of constipation, CNS
44
45 depression or bleeding.
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52 After adjusting for age, sex and socioeconomic deprivation, those with self-report COPD remained
53
54 more likely to be taking three or more medications in each category than those without COPD. These
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findings remained statistically significant after adjusting for smoking status, alcohol frequency, BMI and physical activity (Table 3). Findings were similar for GOLD COPD however, after adjusting for additional potentially confounding variables, results for bleeding risk were not statistically significant in this sensitivity analysis (Table 3).

Table 3. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs				
ADR	Self-report COPD compared with no COPD N=502,640		GOLD COPD compared with no COPD N=496,943	
	Model 1 N=502,013	Model 2 N=487,718	Model 1 N=496,943	Model 2 N=482,378
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Falls	2.27 (2.13 – 2.42) ***	1.83 (1.71-1.96) ***	1.66 (1.47 – 1.87) ***	1.49 (1.30-1.69) ***
Constipation	2.71 (2.54 – 2.89) ***	2.66 (2.39-2.96) ***	2.18 (1.77 – 2.64) ***	1.82 (1.47-2.24) ***
Urinary retention	3.38 (2.94 – 3.87) ***	2.59 (2.22-3.0) ***	1.98 (1.44 – 2.64) ***	1.64 (1.18-2.21) **
CNS depression	3.75 (3.31 – 4.25) ***	2.81 (2.45-3.22) ***	2.29 (1.73 – 2.95) ***	1.87 (1.40-2.43) ***
Bleeding	4.60 (3.35 – 6.19) ***	3.39 (2.40-4.66) ***	2.63 (1.25 – 4.80) **	1.76 (0.75-3.48) §
Renal injury	2.22 (1.86 – 2.62) ***	1.84 (1.53-2.19) ***	1.94 (1.41 – 2.58) ***	1.84 (1.33-2.49) ***

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
 Model 1: Adjusted for age, sex and socioeconomic status
 Model 2: Adjusted for age, sex, socioeconomic status, smoking, alcohol frequency, body mass index and physical activity

Finally, each category of ADR risk was assessed in a subgroup analysis for each category of LTC (cardiovascular, GI, cancer, mental health and painful conditions/inflammatory arthropathies) comparing those with and without COPD (e.g. participants with cardiovascular disease plus COPD compared with participants with cardiovascular disease alone, etc.). These models were adjusted for age, sex and socioeconomic status only. Within each category of LTC, those with self-reported COPD were more likely to be at risk of each ADR than those without COPD (appendix 3). Not all results were statistically significant when using GOLD COPD (Appendix 3).

DISCUSSION

Summary of main findings

Multimorbidity and polypharmacy in COPD were common among UK Biobank participants. The presence of multimorbidity was highly prevalent in those with COPD (85%). More than half (52%) reported polypharmacy (five or more medications), and 15% reported 10 or more medications. The prevalence of cardiovascular disease, as well as the degree of polypharmacy, was higher among those with more severe airflow obstruction.

For the first time, our data demonstrates that those with COPD were more likely than those without to be prescribed multiple medications (\geq three) with similar ADRs. Those with COPD plus cardiovascular disease were most likely to be taking multiple medications associated with increased risk of falls or renal injury, while those with COPD plus mental health conditions were most likely to be taking medications predisposing to constipation, CNS depression and bleeding.⁽⁵²⁾ Within each category of LTC, those with COPD were more likely to be taking multiple medications with similar ADRs than those without. These associations between patterns of multimorbidity and specific ADR risks have not been described or quantified previously.

Strengths and limitations

Strengths of this study include the large sample size with representation from different areas of the UK. The range of data collected at UK Biobank assessment centres meant it was possible to compare a range of sociodemographic characteristics as well as spirometry data, the latter being unusual for a large community based cohort. It is recognised, however, that UK Biobank participants show some evidence of 'healthy volunteer bias', differing from the UK average on a number of socioeconomic, lifestyle and health-related measures. Specifically they are less socioeconomically deprived, less likely to smoke, to be obese, and have fewer self-reported health conditions.⁽⁵³⁾ All LTC diagnoses

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3 as well as medication data were self-reported, with no alternative means of verification. We
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5 attempted to minimise this limitation by identifying a subset of those with COPD meeting the GOLD
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7 diagnostic criteria and repeating the analyses with this subset. Importantly, spirometry values were
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9 also pre-bronchodilator, which is in contravention to guidelines for diagnosing COPD. Additionally,
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11 information was not available about the strength of indication for medications and individual
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13 susceptibility to risk, which is a limitation when considering the risk of ADRs.
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16 The use of the Scottish Government Polypharmacy Guideline allowed analysis of potential ADR risk
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18 by specific common ADRs. The intended purpose of this guideline, however, was not to identify
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20 potential risk from a population sample, but rather to identify potential causes of symptoms or
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22 complications. The analysis in this study, therefore, serves only as an approximation of potential risk,
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24 not an absolute marker of inappropriate polypharmacy. The cross-sectional nature of this analysis
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26 also precludes an analysis of actual harm as a result of polypharmacy. Many of the potential ADRs,
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28 such as falls and fractures and renal injury, and frequently multifactorial events and may not be
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30 directly attributable to medication use. Despite these limitations, however, the co-prescription of
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32 multiple medications with similar ADRs strongly implies greater potential for harm. The association
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34 of such prescribing patterns with COPD, across a range of potential ADRs, is clear from our findings.
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36 This analysis is, to the author's knowledge, the first to attempt to quantify this risk for specific ADRs
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38 in this way.
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45 **Context and implications**

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48 The increased prevalence of individual LTCs such as coronary heart disease, hypertension, diabetes,
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50 dyspepsia, osteoporosis, cancer, depression and anxiety in those with COPD is similar to the findings
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52 from other population based studies of multimorbidity in COPD.(5, 11, 54-56) Our finding that
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54 cardiovascular disease prevalence increased with increasing severity of COPD is in keeping with the
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3 body of literature on cardiovascular disease and COPD, in which high prevalence has been observed
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5 in (usually older) cohorts with severe airflow limitation.(5, 21) Greater polypharmacy with greater
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7 severity of COPD has also been observed previously in older COPD populations,(43, 57) although
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9 such analyses have been smaller (n=1859 and 398, respectively) and have not assessed the specific
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11 patterns of prescribing in COPD. To the best of our knowledge, no previous studies have assessed
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13 the risk of ADRs as a result of polypharmacy in COPD. A recent population-based analysis of
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15 prescribing data from 310,000 adults in Scotland showed that over 15 years from 1995 to 2010 the
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17 proportion of people with polypharmacy and with potentially serious drug-to-drug interactions
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19 increased dramatically.(37) The number of prescribed medications was also associated with
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21 increased risk of interactions. Our analysis differs in approach from this analysis, by seeking to
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23 identify patterns of prescribing increasing risk of specific adverse events, rather than counting total
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25 potential interactions. The strength of our approach lies in highlighting specific patterns of
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27 multimorbidity in which specific ADRs are more likely. Our findings can therefore be applied to
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29 clinical practice, highlighting the importance of recognising multimorbidity in COPD and being alert
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31 to specific ADRs when prescribing medication.
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38 Our findings indicate that in those with COPD the potential for ADRs as a result of combinations of
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40 medications is high, and this appears to be the result of a high prevalence of extra-pulmonary LTCs.
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42 Clinical guidelines for COPD should place greater emphasis on the need for assessment of associated
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44 multimorbidity and the risk of associated ADRs. While our analysis shows potential areas where ADR
45
46 risk exists in COPD (e.g. falls in those with concomitant cardiovascular disease, CNS depression,
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48 constipation with concomitant mental health conditions), future research is merited to assess what
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50 actual harm could be attributed to such prescribing patterns.
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53 **Conclusion**

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3 Among UK Biobank participants with COPD there was considerable multimorbidity and
4 polypharmacy. Those with COPD were highly likely to be concurrently prescribed multiple
5 medications with similar potential adverse effects. Medications contributing to this risk were
6 largely indicated for the management of the associated morbidities rather than COPD. Future
7 research should examine the effects on healthcare outcomes of co-prescribing of multiple drugs
8 with similar potential of ADRs. Clinical guidelines for COPD should emphasise the need for
9 assessment of multimorbidity and the risk of associated ADRs.
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21 **Figure Legends**

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24 **Figure 1:** Flow diagram of identification of participants with 'self-report COPD' and 'GOLD COPD'.
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27 **Figure 2:** Bubble plot showing percentage of participants in each comorbidity category taking 3 or
28 more concomitant medications associated with specific adverse drug reactions.
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31 32 33 34 35 36 37 **Ethics approval and consent to participate**

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40 Participants provided full informed consent to participate in UK Biobank and this study was covered
41 by the generic ethical approval for UK Biobank studies from the NHS National Research Ethics
42 Service (Ref 16/NW/0274).
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50 **Availability of data and materials**

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53 UK Biobank data is available via www.ukbiobank.ac.uk. Syntax for the generation of derived
54 variables and for the analysis used for this study will be submitted to UK Biobank for record.
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Competing interests

The authors declare that they have no competing interests

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Author contributions

All authors (PH, BN, BJ, RM, DL, KG and FM) were involved in the conceptualisation and design of the project and interpretation of results. PH carried out the analysis with support from BJ, RM and BN. DL provided statistical support. All authors had access to the data. PH wrote the first draft of the paper and all authors commented on subsequent drafts. All authors approved the final draft for publication. FM is guarantor.

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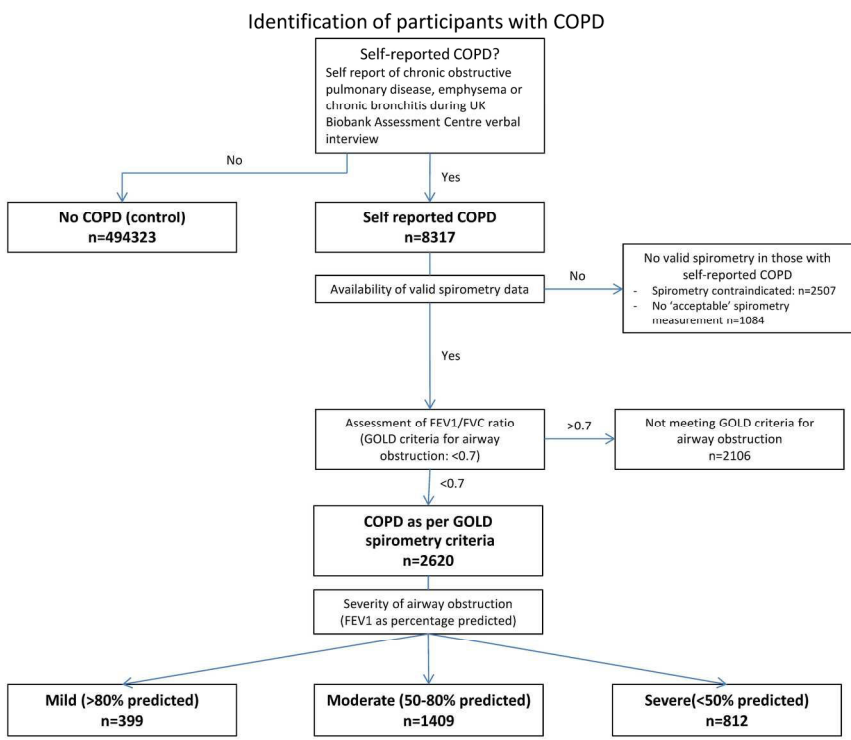
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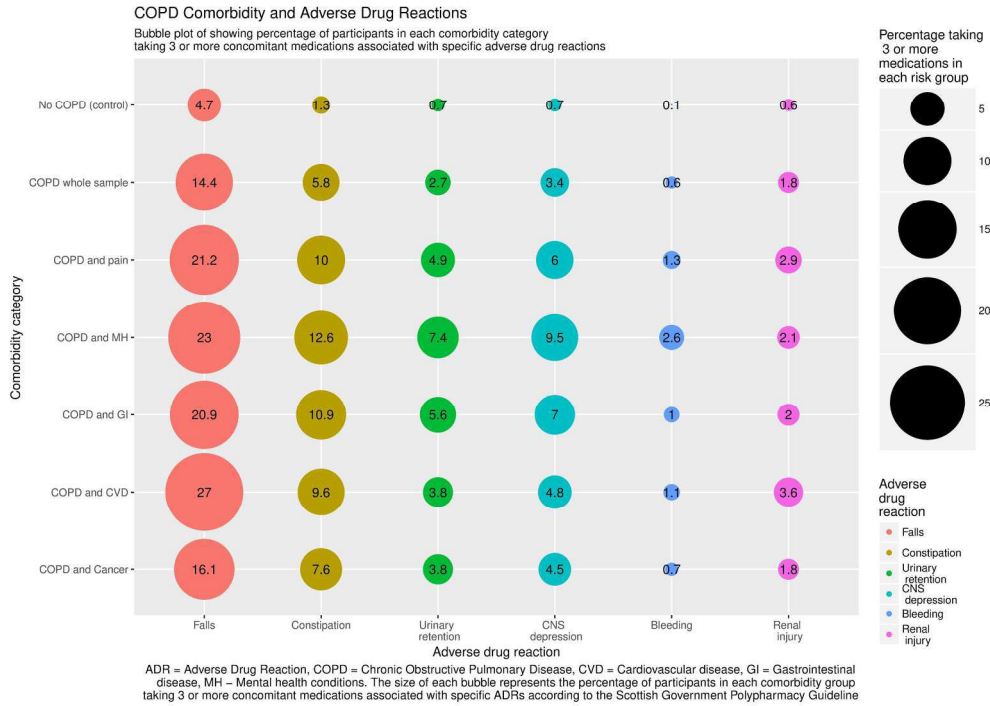
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Flow diagram of identification of participants with 'self-report COPD' and 'GOLD COPD'.

190x142mm (300 x 300 DPI)



Bubble plot showing percentage of participants in each comorbidity category taking 3 or more concomitant medications associated with specific adverse drug reactions.

209x148mm (300 x 300 DPI)

Comorbidity category (used in analysis)	Conditions included (as reported in table 2)	Self-reported conditions comprising this condition (UK Biobank variables used to identify self-reported conditions)
Cardiovascular conditions	Hypertension	Hypertension Essential hypertension
	Coronary heart disease	Heart attack/MI Angina
	Diabetes	Diabetic nephropathy Diabetic neuropathy/ulcers Diabetes Type 1 diabetes Type 2 diabetes Diabetic eye disease
	Stroke/TIA	Stroke TIA Subarachnoid haemorrhage Brain haemorrhage Ischaemic stroke
	Atrial fibrillation	Atrial fibrillation
	Heart failure	Cardiomyopathy Hypertrophic cardiomyopathy Heart failure/pulmonary oedema
	Peripheral vascular disease	Peripheral vascular disease Leg claudication/intermittent claudication
Respiratory	COPD	COPD/Chronic obstructive pulmonary disease Emphysema/Chronic bronchitis Emphysema
	Asthma	Asthma
	PE/DVT	Deep vein thrombosis Pulmonary embolism
	Bronchiectasis	Bronchiectasis
	Pulmonary fibrosis	Pulmonary fibrosis
Cancer	Cancer	"yes"/"no" to "have you ever had cancer?"
Gastrointestinal	Dyspepsia	Gastro-oesophageal reflux (GORD) Oesophagitis/Barrett's oesophagus Gastric stomach ulcers Gastric erosions/gastritis Duodenal ulcer Dyspepsia/indigestion Hiatus hernia Helicobacter pylori
	Diverticular disease	Diverticular disease/diverticulitis

	Irritable bowel syndrome	Irritable bowel syndrome
	Chronic liver disease	Oesophageal varices Non infective hepatitis Liver failure/cirrhosis Primary biliary cirrhosis
	Inflammatory bowel disease	Inflammatory bowel disease Crohn's disease Ulcerative colitis
	Constipation	Constipation
	Viral hepatitis	Hepatitis B Hepatitis C Hepatitis D
Mental Health	Depression	Depression Postnatal depression
	Anxiety	Anxiety/panic attacks Nervous breakdown Post-traumatic stress disorder Obsessive compulsive disorder Stress Insomnia Psychological/psychiatric problem
	Schizophrenia	Schizophrenia
	Bipolar	Mania Bipolar disorder Manic depression
Painful conditions	Connective tissue diseases	Myositis/myopathy Systemic lupus erythematosus/SLE Connective tissue disorder Sjogren's syndrome.sicca syndrome Dermatopolymyositis Scleroderma/systemic sclerosis Rheumatoid arthritis Psoriatic arthropathy Dermatomyositis Polymyositis Polymyalgia rheumatica
	Other painful conditions	Back pain Joint pain Headaches (not migraine) Sciatica Plantar fasciitis Carpal tunnel syndrome Fibromyalgia Arthritis Shingles Disc problem Prolapsed disc/slipped disc

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		Spine arthritis/spondylitis Ankylosing spondylitis Back problem Osteoarthritis Gout Cervical spondylosis Trigeminal neuralgia Disc degeneration Trapped nerve/compressed nerve
Other	Osteoporosis	Osteoporosis

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Drugs with cumulative risk of Adverse Drug Reactions*	
Adverse Drug Reaction	Contributing drug classes (participants taking 3 or more considered 'at risk' for the purposes of analysis)
Falls	H2-receptor blockers Loperamide Prochlorperazine Metoclopramide ACE-inhibitor/Angiotensin receptor blocker Thiazide diuretic Loop diuretic Amiloride/triamterene Spironolactone Beta-blocker Calcium-channel blocker Nitrates or nicorandil Digoxin Oral steroids Opiates Benzodiazepines Sedative antihistamines H1-receptor blockers Antipsychotics Tricyclic antidepressants Sulfonylureas/gliptins/glinides Pioglitazone Urinary antispasmodics Dosulepin Alpha-blockers
Constipation	H2-receptor blockers Laxatives Loperamide Prochlorperazine Thiazide diuretics Loop diuretics Calcium-channel blockers Opiates Sedative antihistamines H1-receptor blockers Antipsychotics Tricyclic antidepressants Urinary antispasmodics Dosulepin
Urinary retention	H2-receptor blockers Loperamide Prochlorperazine Opiates Sedative antihistamines H1-receptor blockers Antipsychotics Tricyclic antidepressants

	Urinary antispasmodics Dosulepin
CNS depression	H2-receptor blockers Loperamide Prochlorperazine Oral steroids Opiates Benzodiazepines Sedative antihistamines H1-receptor blockers Antipsychotics Tricyclic antidepressants Urinary antispasmodics Dosulepin
Bleeding	Aspirin Clopidogrel Other antiplatelets Oral steroids SSRIs and related drugs Non-steroidal anti-inflammatory drugs Warfarin
Renal injury	ACE-inhibitor/angiotensin receptor blockers Thiazide diuretic Loop diuretic Amiloride/triamterene Spironolactone Antibiotics/antifungals Non-steroidal anti-inflammatory drugs
Adapted from <i>Scottish Government Model of Care Polypharmacy Working Group. Polypharmacy Guidance (2nd edition) March 2015. Scottish Government.</i>	

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Comorbidity category	Self-report COPD compared with no COPD N=502,640		GOLD COPD compared with no COPD N=496,943	
	Model 1 N=502,013	Model 2 N=487,718	Model 1 N=496,324	Model 2 N=482,378
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Cardiovascular disease	1.45 (1.39-1.52) ***	1.28 (1.22-1.34) ***	1.11 (1.02-1.20) *	1.08 (0.99-1.18) §
Cancer	1.29 (1.20-1.39) ***	1.22 (1.13-1.31) ***	1.12 (0.99-1.27) §	1.06 (0.92-1.19) §
Gastrointestinal disease	1.76 (1.67-1.86) ***	1.56 (1.48-1.65) ***	1.4 (1.26-1.54) ***	1.24 (1.12-1.38) ***
Mental health	2.02 (1.89-2.15) ***	1.62 (1.51-1.73) ***	1.75 (1.54-1.97) ***	1.40 (1.22-1.58) ***
Painful conditions	1.62 (1.55-1.70) ***	1.41 (1.34-1.48) ***	1.40 (1.28-1.52) ***	1.24 (1.13-1.35) **

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
 Model 1: Adjusted for age, sex and socioeconomic status
 Model 2: Adjusted for age, sex, socioeconomic status, smoking, alcohol frequency, body mass index and physical activity

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Outcome	Self-report COPD compared with no COPD N=502,640		GOLD COPD compared with no COPD N=496,943	
	Model 1 N=502,013	Model 2 N=487,718	Model 1 N=496,324	Model 2 N=482,378
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Multimorbidity (≥4 conditions)	3.49 (3.28-3.70) ***	2.79 (2.61-2.98) ***	2.34 (2.10-2.63) ***	1.99 (1.75-2.25) ***
Polypharmacy (≥5 medications)	3.85 (3.68-4.03) ***	3.30 (3.15-3.46) ***	3.47 (3.20-3.75) ***	3.20 (2.95-3.48) ***
Polypharmacy (≥10 medications)	5.72 (5.36-6.10) ***	4.42 (4.11-4.75) ***	4.20 (3.72-4.73) ***	3.56 (3.12-4.05) ***

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
 Model 1: Adjusted for age, sex and socioeconomic status
 Model 2: Adjusted for age, sex, socioeconomic status, smoking, alcohol frequency, body mass index and physical activity

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ADR	Self-report COPD compared with no COPD N=502,640		GOLD COPD compared with no COPD N=496,943	
	Model 1 N=502,013	Model 2 N=487,718	Model 1 N=496,943	Model 2 N=482,378
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Falls	2.27 (2.13 – 2.42) ***	1.83 (1.71-1.96) ***	1.66 (1.47 – 1.87) ***	1.49 (1.30-1.69) ***
Constipation	2.71 (2.54 – 2.89) ***	2.66 (2.39-2.96) ***	2.18 (1.77 – 2.64) ***	1.82 (1.47-2.24) ***
Urinary retention	3.38 (2.94 – 3.87) ***	2.59 (2.22-3.0) ***	1.98 (1.44 – 2.64) ***	1.64 (1.18-2.21) **
CNS Depression	3.75 (3.31 – 4.25) ***	2.81 (2.45-3.22) ***	2.29 (1.73 – 2.95) ***	1.87 (1.40-2.43) ***
Bleeding	4.60 (3.35 – 6.19) ***	3.39 (2.40-4.66) ***	2.63 (1.25 – 4.80) **	1.76 (0.75-3.48) §
Renal injury	2.22 (1.86 – 2.62) ***	1.84 (1.53-2.19) ***	1.94 (1.41 – 2.58) ***	1.84 (1.33-2.49) ***

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
 Model 1: Adjusted for age, sex and socioeconomic status
 Model 2: Adjusted for age, sex, socioeconomic status, smoking, alcohol frequency, body mass index and physical activity

Subgroup analyses – comparing COPD with no COPD among participants with specific categories of comorbidity

Table S4. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with cardiovascular disease (CVD)

ADR	Self-report COPD plus CVD compared with CVD alone (no COPD) N=156,848	GOLD COPD plus CVD compared with CVD alone (no COPD) N=154,047
	Model 1 N=156,667	Model 1 N=153,852
	OR (95% CI)	OR (95% CI)
Falls	1.92 (1.79-2.07) ***	1.59 (1.39-1.82) ***
Constipation	2.89 (2.58-3.23) ***	2.06 (1.63-2.57) ***
Urinary retention	2.78 (2.33-3.28) ***	1.92 (1.30-2.72) ***
CNS Depression	3.17 (2.71-3.69) ***	2.17 (1.54-2.97) ***
Bleeding	4.00 (2.85-5.48) ***	2.26 (0.96-4.44) *
Renal injury	1.90 (1.59-2.25) ***	1.82 (1.31-2.45) ***

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
Model 1: Adjusted for age, sex and socioeconomic status

Table S5. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with cancer

ADR	Self-report COPD plus cancer compared with cancer alone (no COPD) N=38,623	GOLD COPD plus cancer compared with cancer alone (no COPD) N=37,958
	Model 1 N=38,575	Model 1 N= 37,912
	OR (95% CI)	OR (95% CI)
Falls	2.35 (1.95-2.81) ***	1.49 (1.00-2.13) *
Constipation	3.55 (2.73-4.56) ***	2.21 (1.22-3.68) **
Urinary retention	3.65 (2.52-5.13) ***	1.99 (0.78-4.14) §
CNS Depression	3.74 (2.66-5.14) ***	2.04 (0.86-4.04) §
Bleeding	4.69 (1.91-9.86) ***	2.20 (0.12-10.23) §
Renal injury	2.0 (1.17-3.20) **	2.26 (0.89-4.71) §

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
Model 1: Adjusted for age, sex and socioeconomic status

Table S6. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with gastrointestinal disease (GI)

ADR	Self-report COPD plus GI compared with GI alone (no COPD) N=58372	GOLD COPD plus GI compared with GI alone (no COPD) N=57103
	Model 1 N=58,299	Model 1 N=57,031
	OR (95% CI)	OR (95% CI)
Falls	2.18 (1.92-2.46) ***	1.46 (1.13-1.87) **
Constipation	2.70 (2.29-3.16) ***	1.58 (1.08-2.24) *
Urinary retention	2.64 (2.12-3.26) ***	1.46 (0.83-2.37) §
CNS Depression	3.02 (2.47-3.66) ***	1.50 (0.88-2.37) §
Bleeding	3.88 (2.27-6.25) ***	3.18 (0.97-7.63) §
Renal injury	1.99 (1.37-2.80) ***	1.22 (0.48-2.51) §

§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001
Model 1: Adjusted for age, sex and socioeconomic status

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Table S7. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with mental health conditions (MH)		
ADR	Self-report COPD plus MH compared with MH alone (no COPD) N=36,949	GOLD COPD plus MH compared with MH alone (no COPD) N=36126
	Model 1 N=36,885	Model 1 N=36,065
	OR (95% CI)	OR (95% CI)
Falls	2.21 (1.90-2.56) ***	1.35 (0.99-1.82) §
Constipation	2.33 (1.93-2.81) ***	1.62 (1.08-2.34) *
Urinary retention	2.17 (1.71-2.74) ***	1.42 (0.82-2.29) §
CNS Depression	2.53 (2.04-3.12) ***	1.66 (1.03-2.54) *
Bleeding	2.86 (1.77-4.17) ***	1.94 (0.76-4.05) §
Renal injury	1.86 (1.19-2.79) **	1.27 (0.45-2.80) §
§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001 Model 1: Adjusted for age, sex and socioeconomic status		

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Table S8. Odds ratios (with 95% CI) for taking 3 of more medications associated with similar ADRs in participants with painful conditions		
ADR	Self-report COPD plus painful conditions compared with painful conditions alone (no COPD) N=83,992	GOLD COPD plus painful conditions compared with painful conditions alone (no COPD) N=82,388
	Model 1 N=83,895	Model 1 N=82,294
	OR (95% CI)	OR (95% CI)
Falls	1.99 (1.79-2.19) ***	1.45 (1.19-1.75) ***
Constipation	2.54 (2.21-2.91) ***	1.50 (1.10-2.00) **
Urinary retention	2.46 (2.03-2.96) ***	1.11 (0.64-1.75) §
CNS Depression	2.71 (2.28-3.21) ***	1.40 (0.90-2.06) §
Bleeding	3.50 (2.37-5.01) ***	2.20 (0.86-4.54) §
Renal injury	1.66 (1.30-2.09) ***	1.49 (0.93-2.25) §
§ : p>0.05 * : p<0.05, ** : p<0.01, *** : p<0.001 Model 1: Adjusted for age, sex and socioeconomic status		

Appendix 4: Specific medications in UK Biobank participants with and without COPD						
Medications	Control n=494323 count (%)	Self-report COPD n=8317 count (%)	GOLD COPD			
			All n=2620 count (%)	Mild n=399 count (%)	Moderate n=1409 count (%)	Severe n= 812 count (%)
Total number of medications						
≥1	356406 (72.1)	7670 (92.2)	2452 (93.6)	352 (88.2)	1321 (93.8)	779 (95.9)
≥5	87286 (17.7)	4312 (51.8)	1349 (51.5)	171 (42.9)	702 (49.8)	476 (58.6)
≥10	10678 (2.2)	1269 (15.3)	329 (12.6)	31 (7.8)	172 (12.2)	126 (15.5)
Respiratory						
Short acting B ₂ agon.	22615 (4.6)	3328 (40.0)	1245 (47.5)	123 (30.8)	614 (43.6)	508 (62.6)
LABA	9819 (2.0)	2357 (28.3)	905 (34.5)	93 (23.3)	411 (29.2)	401 (49.3)
LAMA	597 (0.1)	1345 (16.2)	581 (22.2)	33 (8.3)	265 (18.8)	283 (34.9)
ICS	15309 (3.1)	2638 (31.7)	962 (36.7)	98 (24.6)	471 (33.4)	393 (48.4)
LABA+ICS	7259 (1.5)	1842 (22.1)	699 (26.7)	67 (16.8)	313 (22.2)	319 (39.3)
Prednisolone	3127 (0.6)	280 (3.4)	82 (3.1)	12 (3.0)	27 (1.9)	43 (5.3)
Mucolytic	174 (0.04)	187 (2.2)	49 (1.9)	1 (0.3)	10 (0.7)	38 (4.7)
Cardiovascular						
Antiplatelet	21817 (4.4)	894 (10.7)	268 (10.2)	31 (7.8)	158 (11.2)	79 (9.7)
ACE-inhibitor	44991 (9.1)	1276 (15.3)	367 (14.0)	33 (8.3)	198 (14.1)	136 (16.7)
ARB	17911 (3.6)	565 (6.8)	159 (6.1)	17 (4.3)	83 (5.9)	59 (7.2)
Calcium CB	14317 (2.9)	627 (7.5)	196 (7.5)	23 (5.8)	106 (7.5)	67 (8.3)
Statin	73439 (14.9)	2278 (27.4)	707 (27.0)	72 (18.0)	395 (28.0)	240 (29.6)
GTN	4425 (0.9)	373 (4.5)	110 (4.2)	8 (2.0)	70 (5.0)	32 (3.9)
ISMN	2814 (0.6)	244 (2.9)	68 (2.6)	5 (1.3)	42 (3.0)	21 (2.6)
Loop diuretic	4836 (1.0)	415 (5.0)	107 (4.1)	10 (2.5)	51 (3.6)	46 (5.7)
Thiazide	21961 (4.4)	637 (7.7)	196 (7.5)	22 (5.5)	108 (7.7)	66 (8.1)
Warfarin	4934 (1.0)	238 (2.9)	67 (2.6)	6 (1.5)	33 (2.3)	28 (3.4)
Diabetes						
Insulin	4643 (0.9)	161 (1.9)	35 (1.3)	2 (0.5)	23 (1.6)	3 (0.4)
Metformin	13754 (2.8)	448 (5.4)	102 (3.9)	7 (1.8)	57 (4.0)	38 (4.7)
Sulphonylurea	4901 (1.0)	158 (1.9)	35 (1.3)	2 (0.5)	17 (1.2)	16 (2.0)
Thiazolidindione	2212 (0.4)	60 (0.7)	17 (0.6)	1 (0.3)	10 (0.7)	6 (0.7)
Gastrointestinal						
PPI	42012 (8.5)	1989 (23.9)	522 (19.9)	79 (19.8)	286 (20.3)	157 (19.3)
Antacid	2435 (0.5)	146 (1.8)	25 (1.0)	7 (1.8)	10 (0.7)	8 (1.0)
H ₂ RA.	7772 (1.6)	325 (3.9)	89 (3.4)	15 (3.8)	53 (3.8)	21 (2.6)
Laxative	5787 (1.8)	317 (3.8)	81 (3.1)	11 (2.8)	40 (2.8)	30 (3.7)
Pain						
Paracetamol	82376 (16.7)	2752 (33.1)	790 (30.2)	111 (27.8)	446 (31.6)	233 (28.7)
NSAID	45909 (9.3)	1149 (13.8)	319 (12.2)	50 (12.5)	175 (12.4)	94 (11.6)
Weak opiate	18736 (3.8)	1209 (14.5)	336 (12.8)	48 (12.0)	191 (13.6)	97 (11.9)
Strong opiate	1071 (0.2)	106 (1.8)	32 (1.2)	5 (1.3)	16 (1.1)	11 (1.4)
Mental health						
SSRI+related	15394 (3.1)	747 (9.0)	175 (6.7)	31 (7.8)	100 (7.1)	44 (5.4)
Tricyclic	4229 (0.9)	206 (2.5)	49 (1.9)	11 (2.8)	25 (1.8)	13 (1.6)
Antipsychotic	2237 (0.5)	107 (1.3)	30 (1.1)	5 (1.3)	16 (1.1)	9 (1.1)
Benzodiazepine	2316 (0.5)	182 (2.2)	47 (1.8)	6 (1.5)	28 (2.0)	13 (1.6)
Metabolic						
Thyroxine	20980 (4.2)	560 (6.7)	150 (5.7)	27 (6.8)	92 (6.5)	31 (3.8)
Bisphosphonate	3655 (0.7)	189 (2.3)	66 (2.5)	15 (3.8)	32 (2.3)	19 (2.3)

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	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5,6,9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
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	6-8
Bias	9	Describe any efforts to address potential sources of bias	14,15
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7,8,9
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8-10
		(b) Describe any methods used to examine subgroups and interactions	9,10
		(c) Explain how missing data were addressed	10
		(d) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	9,10
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11, figure 1
		(b) Give reasons for non-participation at each stage	11, Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	11-13, figure 2, appendix 3
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	11-13, figure 2, appendix 3
		(b) Report category boundaries when continuous variables were categorized	12,13
		(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	12,13, Appendix 3,
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
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	14,15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15,16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15,16,17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17,18

*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.