Elsevier Editorial System(tm) for JAMDA
Manuscript Draft

Manuscript Number: JAMDA-D-19-00288R2

Title: IMPORTANCE OF FRAILTY FOR ASSOCIATION OF ANTIPSYCHOTIC DRUG USE WITH RISK OF FRACTURE. COHORT STUDY USING ELECTRONIC HEALTH RECORDS

Article Type: Original Study

Keywords: Fractures, bone; frailty; antipsychotic agents; primary care; electronic health records; dementia.

Corresponding Author: Professor Martin C Gulliford, FRCP

Corresponding Author's Institution: King's College London

First Author: Rafael Gafoor, PhD

Order of Authors: Rafael Gafoor, PhD; Judith Charlton, MSc; Rathi Ravindrarajah, PhD; Martin C Gulliford, FRCP

Abstract: Objective: To evaluate association of first- or second-generation antipsychotic drugs with fracture risk at different levels of frailty over the age of 80 years.
Design: Population-based cohort study.
Setting and Participants: UK Clinical Practice Research Datalink (CPRD) including 153,304 patients aged 80 years and older between 2006 and 2015.
Methods: Rates of fracture and adjusted rate ratios (RR) were estimated by antipsychotic (AP) drug exposure category, adjusting for age, gender, frailty, number of deficits and dementia diagnosis.
Results: Data were analysed for 165,726 treatment episodes (153,304 patients; 61.3% women; mean age 83 years; 21,365 fractures; 681,221.1 person-years of follow-up). AP exposure was associated with increasing age, frailty and dementia diagnosis. After adjusting for frailty and covariates, first-generation AP exposure was associated with risk of any fracture, RR 1.24 (95% confidence interval 1.07 to 1.43, P=0.003). Second-generation AP exposure was associated with femur fracture (RR 1.41, 1.22 to 1.64, P<0.001) but less strongly with any fracture (RR 1.12, 1.01 to 1.24, P=0.033). Fracture incidence increased with frailty level. The number of person-years of first-generation AP treatment associated with one additional fracture at any site was 75 (42 to 257) for severely frail patients but 187 (95% CI 104 to 640) for 'fit' patients. For second-generation AP, one additional femur fracture might result from 173 (111 to 323) person-years treatment in severe frailty but 365 (234 to 681) person-years treatment for 'fit' patients.
Conclusions and Implications: Frail patients are more likely to receive antipsychotic drug treatment but their absolute risk of AP-associated fracture is substantially greater than for non-frail patients.

*Title Page (Containing author details)

IMPORTANCE OF FRAILTY FOR ASSOCIATION OF ANTIPSYCHOTIC DRUG USE WITH RISK OF FRACTURE. COHORT STUDY USING ELECTRONIC HEALTH RECORDS

Rafael Gafoor PhD,[a] Judith Charlton MSc,[a] Rathi Ravindrarajah PhD,[a,b] Martin C Gulliford MA[a,c]

[a]School of Population Health and Environmental Sciences, King's College London; [b]University of Manchester, Centre for Primary Care, Division of Population Health, Health Services Research and Primary Care; [c]NIHR Biomedical Research Centre at Guy's and St Thomas' Hospitals London

Short title: Antipsychotic drugs, frailty and fracture

Correspondence: **Martin Gulliford**
Addison House, Guy's Campus,
King's College London,
London SE1 1UL
Tel: +44 207 848 6631
Fax: +44 207 848 6620
Email: martin.gulliford@kcl.ac.uk

Word count: **Abstract: 258 words**
Text: 3,781
Tables: 3
Figures: 2

Key words: Fractures, bone; frailty; antipsychotic agents; primary care; electronic health records; dementia.

Brief Summary

Use of antipsychotic drugs at older ages may be associated with fracture. This study shows that the absolute risk of fracture is greatest in frail patients, who are more likely to be prescribed antipsychotic drugs.

Acknowledgement

The study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the authors alone. MG was supported by the NIHR Biomedical Research Centre at Guy's and St Thomas' Hospitals. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. The authors have no conflicts of interest.

IMPORTANCE OF FRAILTY FOR ASSOCIATION OF ANTIPSYCHOTIC DRUG USE WITH RISK OF FRACTURE. COHORT STUDY USING ELECTRONIC HEALTH RECORDS

ABSTRACT

Objective: To evaluate association of first- or second-generation antipsychotic drugs with fracture risk at different levels of frailty over the age of 80 years.

Design: Population-based cohort study.

Setting and Participants: UK Clinical Practice Research Datalink (CPRD) including 153,304 patients aged 80 years and older between 2006 and 2015.

Methods: Rates of fracture and adjusted rate ratios (RR) were estimated by antipsychotic (AP) drug exposure category, adjusting for age, gender, frailty, number of deficits and dementia diagnosis.

Results: Data were analysed for 165,726 treatment episodes (153,304 patients; 61.3% women; mean age 83 years; 21,365 fractures; 681,221.1 person-years of follow-up). AP exposure was associated with increasing age, frailty and dementia diagnosis. After adjusting for frailty and covariates, first-generation AP exposure was associated with risk of any fracture, RR 1.24 (95% confidence interval 1.07 to 1.43, P=0.003). Second-generation AP exposure was associated with femur fracture (RR 1.41, 1.22 to 1.64, P<0.001) but less strongly with any fracture (RR 1.12, 1.01 to 1.24, P=0.033). Fracture incidence increased with frailty level. The number of person-years of first-generation AP treatment associated with one additional fracture at any site was 75 (42 to 257) for severely frail patients but 187 (95% CI 104 to 640) for 'fit' patients. For second-generation AP, one additional femur fracture might result from 173 (111 to 323) person-years treatment in severe frailty but 365 (234 to 681) person-years treatment for 'fit' patients.

Conclusions and Implications: Frail patients are more likely to receive antipsychotic drug treatment but their absolute risk of AP-associated fracture is substantially greater than for non-frail patients.

[258 words]

INTRODUCTION

People aged more than 80 years represent the fastest growing sector of the population in high-income countries[1] with multiple morbidities and impairments representing key drivers of health care utilisation and costs.[2] Cognitive decline and dementia increase rapidly in frequency with age. In 2009, there were estimated to be 700,000 people in the UK with dementia; a number estimated to double within 30 years.[3] Patients with cognitive decline and dementia often manifest symptoms of agitation, aggression, shouting, sleep disturbance and depression which form part of the constellation of Behavioural and Psychological Symptoms in Dementia (BPSD). Approximately 90% of patients with dementia will exhibit symptoms of BPSD at some point in their illness.[4] Delirium and acute states of confusion are also common in older people particularly during episodes of acute illness.[5] These distressing symptoms have been commonly managed by the administration of antipsychotic drugs. 'First-generation' (or 'typical') antipsychotics, including haloperidol and thioridazine, target the dopaminergic system and are often associated with marked anticholinergic side effects. The introduction of the 'second-generation' (or 'atypical') antipsychotics was considered to allow prescribers the opportunity to treat behavioural and psychological symptoms while reducing the risk of side effects.[6]

Trials of second generation antipsychotic drugs raised concerns that these drugs may be associated with increased risks of stroke and mortality.[7] A 2006 meta-analysis found that second-generation antipsychotic drugs were associated with increased risk of cerebrovascular events but there was no evidence for increase in falls or injuries.[7] This conclusion was endorsed by a 2009 report prepared for the English Department of Health,[8] which discouraged the use of antipsychotic drugs in older people in general, and those with dementia in particular.[8] The report concluded that second-generation antipsychotic drugs were associated with increased risk of stroke and mortality but not with risk of falls or fractures.[8] A recent study using primary care electronic records from UK family practices

found that, while there has been a reduction in use of first-generation antipsychotic drugs, second-generation AP drugs continue to be widely prescribed to patients with diagnoses of dementia.[9]

First-generation antipsychotics (because of their propensity to provoke Parkinsonian symptoms due to extra-pyramidal dopaminergic blockade) as well as second-generation antipsychotics (due to their marked sedative properties in general) both potentially increase the risk of falls in the elderly. Several epidemiological studies have now evaluated the risk of fracture during treatment with antipsychotic drugs. A recent systematic review of 19 cohort studies,[10] found that first-generation AP drugs were associated with increased risk of hip fracture, with a pooled odds ratio of 1.67 (95% confidence interval 1.45 to 1.93), while the risk was lower with second-generation AP drugs, pooled odds ratio 1.33 (1.11 to 1.58). These findings suggest that the safety profile of first- and second-generation antipsychotic drugs can be expected to vary for different adverse events; fracture potentially represents a greater risk for first-generation drugs, while cardiovascular side effects have been viewed with greater concern for second-generation drugs.

In recent years, there have been advances in the understanding and measurement of age-related frailty as a condition of heightened vulnerability in older people. The frailty concept has no unique definition and can be measured using several different tools.[11] The frailty phenotype draws on the co-occurrence of several non-specific clinical features including weakness, fatigue, weight loss, inactivity and slow walking speed.[12] The frailty index approach evaluates the number of deficits, which may include symptoms, signs, diseases or laboratory measurements.[13] Frailty shows considerable overlap with the concepts of comorbidity and multiple morbidity. In UK Biobank data, people with four or more long term conditions had 27 times higher odds of the frailty phenotype.[14] For the present study we

employed the e-Frailty Index (eFI)[15] because this is readily operationalised into electronic health records.[16] The eFI evaluates the presence of 36 deficits as a proportion of the total possible, leading to a categorisation of 'fit', 'mild', 'moderate' or 'severe' frailty.[15] As evidence of validity, increasing frailty level using the eFI is associated with mortality, hospitalisation or nursing home admission.[15] Frailty status is also associated with the incidence of fragility and non-fragility fractures.[17] The influence of patients' frailty status on the utilisation of AP drugs and risk of fracture is therefore an important clinical concern but this has not been addressed by previous studies. This study aimed to evaluate AP-associated fracture risk in relation to frailty level by conducting a cohort study using electronic health records. We aimed to evaluate patients' treatment with first and second-generation AP drugs according to frailty level; we also aimed to estimate the risk of fragility and non-fragility fractures associated with AP exposure[17] at different levels of frailty measured using the e-Frailty index.[15] We also compared estimates with those obtained using the Charlson comorbidity index for risk stratification.

METHODS

Population and participant selection

A cohort study was conducted using electronic health records from the Clinical Practice Research Datalink (CPRD). The CPRD is one of the world's largest databases of primary care electronic health records, including data from about 7% of UK family practices from 1990 to the present. The CPRD population is generally representative of the UK population and many studies have demonstrated the validity of CPRD data.[18] For the present study, we drew a sample from the January 2018 release of CPRD. We included all 135 CPRD family practices in England that contributed throughout the period between 1st January 2006 and 31st December 2017. We then selected participants who were aged 80 years or older during

this 12-year period. Participant records were evaluated from 1st January in the year the participant turned 80 years (because only years of birth are available in CPRD). Records were analysed between the latest of 1st January 2006, or the patient start of record, and the earliest of the patient's death date, end of registration or 31st December 2017. The use of anonymised health records for this study was approved by the CPRD Independent Scientific Advisory Committee (ISAC protocol number 17_272R).

Main measures

Participant records were evaluated for prescriptions of antipsychotic drugs. Based on the British National Formulary (sections 4.2.1 and 4.2.2), antipsychotic drugs were classified into first-generation drugs (including benperidol, chlorpromazine, chlorprothixene, flupentixol, fluphenazine, fluspirilene, haloperidol, loxapine, oxypertine, pericyazine, perphenazine, pimozide, pipotiazine, prochlorperazine, promazine, sulpiride, thioridazine, trifluoperazine, zuclopenthixol) and second-generation drugs (including amisulpride, aripiprazole, clozapine, lurasidone hydrochloride, olanzapine, paliperidone, quetiapine, remoxipride, risperidone, sertindole, zotepine). Antipsychotic prescriptions were classified as 'oral', 'depot' or 'other parenteral'. Exact durations of treatment were not explicitly recorded in CPRD, an algorithm was developed as follows. Previous research shows most prescriptions for chronic illness in CPRD have a duration of 90 days,[19] oral prescriptions were therefore assumed to last 90 days, as were depot products. A single parenterally administered dose was assumed to last one day. A ninety-day washout period was allowed in addition. Each patient's record was then divided into treatment episodes including exposed to first-generation antipsychotics, exposed to second-generation antipsychotic drugs or not exposed.

Fracture events were evaluated from medical codes recorded into patients' clinical and referral records. The referral file includes information concerning referrals to hospital and

communications from hospitals after discharge. The codes for fracture were those reported by Ravindrarajah et al.[17] who adapted the categorisation used by Torstensson et al.[20] to categorise fractures into 'non-fragility' and 'fragility' fractures. Fragility fractures most commonly occur in the femur, pelvis, shoulder and upper arm, and forearm and wrist,[20 21] fractures which were not coded into these categories were coded as non-fragility fractures. Incident fractures were those recorded more than 12 months after the start of patients' records. Records of fracture at the same site within a 90-day period were assumed to refer to a single fracture.

Patients' frailty status was evaluated using the e-Frailty Index as reported by Clegg et al.[15] The e-Frailty index is used to classify individuals as 'fit', or having 'mild', 'moderate' or 'severe' frailty based on the occurrence of 36 deficits, including common medical conditions and age-related impairments. The e-Frailty index was adapted for this study by omitting falls and fractures from the list of deficits because fractures were the outcome of interest. Quantitative traits were also omitted as reported previously.[16] Patients' frailty status was estimated for each year of follow-up, using all recorded medical events up to the start of that year. At the peer-review stage, we added the Charlson comorbidity index[22] in order to introduce a more widely-accepted measure as a variable to provide cross-validation of the frailty measure. The Charlson index was evaluated as reported by Khan et al.[23] The Charlson index was analysed using the categories of zero, 1-2, 3-4 and ≥5, as suggested by Charlson et al.[22]

Statistical analysis

Patients' baseline characteristics were tabulated and the associations with utilisation of AP drugs were evaluated using a multiple logistic regression model. Fracture events were linked to antipsychotic treatment episodes using the 'rangejoin' command in Stata version 14.[24]

Incidence rates per 1,000 patient years were estimated. A Poisson model was fitted with the numbers of fractures in each exposure interval as dependent variable, and log of person-years as offset. Robust variance estimates were employed to allow for correlation of treatment episodes within patients. Models were adjusted for age, age-squared, gender, and frailty category. In addition, the number of deficits from the e-Frailty Index in each patient was included as a quantitative predictor in order to minimise the loss of information resulting from categorisation of frailty. Dementia diagnosis was included because of the strong association with AP prescription but other comorbidities were considered to be represented through the number of deficits. Adjusted rate ratios were estimated for all fractures and for sub-groups of fracture including fractures of the femur, pelvis, shoulder and upper arm, and forearm and wrist, as well as non-fragility fractures as reported previously.[17] Frailty index category was cross-tabulated against Charlson comorbidity category. Incidence rates and numbers needed to harm' were calculated for Charlson comorbidity categories.

RESULTS

The cohort initially included 173,688 patients who were registered at 135 family practices in England that contributed data to CPRD throughout the period 2006 to 2017. In order to include incident fracture events only, the 12 months following the start of patient registration were excluded and this resulted in the exclusion of 19,979 patients with insufficient record for analysis. There were 405 patients omitted because both first and second-generation antipsychotic drugs were prescribed in a single treatment episode. There remained 153,304 (88.3%) patients for further analysis. There were 61.3% women with mean age 83 years, range 80 to 114 years.

The 153,304 patients included 143,406 (93.5%) who were never treated with antipsychotic drugs. There were 4,078 (2.7%) patients with one or more treatment episodes with first-generation AP drugs and 5,856 (3.8%) patients with one or more treatment episodes with second-generation AP drugs, including 36 patients with treatment episodes at different times for both first and second-generation drugs.

Figure 1 and Table 1 show the distribution of patient characteristics according to AP treatment category. Compared to patients who were never treated with AP drugs, prescription of both first and second-generation AP drugs was associated with greater age, more advanced frailty status, dementia diagnosis and comorbidity status. For patients with severe frailty the adjusted relative odds of treatment with first-generation AP were 5.55 (4.83 to 6.36, P<0.001) compared to fit patients; for second-generation AP the adjusted relative odds were 3.50 (3.10 to 3.95, P<0.001). Prescription of AP drugs was strongly associated with dementia diagnosis, with adjusted relative odds of 2.68 (2.50 to 2.88, P<0.001) for first-generation and 7.64 (7.21 to 8.09, P<0.001) for second-generation AP drugs, compared with patients with no dementia diagnosis. Prescription of antipsychotic drugs was associated with

Charlson comorbidity category but associations were slightly less strong than for frailty category. Supplementary Table 1 presents a cross-tabulation of the frailty and comorbidity indices, showing strong association between the two metrics. Patients with a Charlson comorbidity category of five or greater had 73.1 (95% confidence interval 63.9 to 83.6) times higher odds of severe frailty than patients with a Charlson comorbidity category of zero.

During a total of 681,221.1 person-years of follow-up, there were 21,365 fractures including 6,380 femoral fractures, 1,258 pelvic fractures, 2,735 forearm fractures, 1,309 fractures of the wrist or hand, 2,928 fractures of the shoulder or upper arm, 6,080 non-fragility fractures and 675 fractures with multiple sites recorded. The overall incidence of fractures was 30.9 per 1,000 person-years without AP exposure; 60.1 per 1,000 during exposure to first-generation AP drugs; and 53.9 per 1,000 during exposure to second-generation AP drugs (Figure 2). After adjusting for age, gender, frailty, number of deficits and dementia diagnosis, the adjusted rate ratio for any fracture compared to no AP exposure was 1.24 (1.07 to 1.43, P=0.003) for first-generation AP drugs and 1.12 (1.01 to 1.24, P=0.033) for second-generation AP drugs (Figure 2). Tests for interaction between AP exposure and frailty category (Supplementary Table 2) gave P=0.164 for first-generation AP drugs and P=0.034 for second-generation AP drugs, for the outcome of all fractures, suggesting only weak evidence of effect modification for the latter class. There was no evidence for a trend of increasing adjusted relative rate of fracture with increasing frailty level for either first- or second-generation AP drugs.

Figure 2 shows the association of AP exposure with fractures at different sites. There was evidence that femur fracture was associated with AP exposure both for first-generation (RR 1.39, 1.12 to 1.74, P=0.003) and second-generation AP drugs (1.41, 1.22 to 1.64, P<0.001). There was evidence that first-generation AP exposure might be associated with fractures of

the pelvis (1.59, 1.01 to 2.52, P=0.044) and wrist and hand (1.82, 1.15 to 2.87, P=0.011). The point estimate was also elevated for multiple fracture sites, though the estimate was imprecise (1.61, 0.79 to 3.29, P=0.190). There was no evidence that second-generation AP drugs were associated with increased risk of fracture at these latter sites. There was no evidence that AP exposure was associated with non-fragility fractures either for first-generation (0.92, 0.67 to 1.26, P=0.595) or second-generation AP drugs (0.92, 0.75 to 1.13, 0.429). An interaction test gave no evidence that the adjusted relative rate of fracture varied by frailty level for femur fracture (Table 2).

Table 2 presents estimates for the 'number needed to harm' (NNH) by frailty level, assuming a causal association. The NNH represents the number of person-years of AP treatment that is associated with one additional fracture. For first-generation AP drugs, the NNH for any fracture was 75 (95% confidence interval 42 to 257) for patients with severe frailty but 187 (105 to 641) for 'fit' patients. The NNH for any fracture associated with second-generation AP drugs was 150 (75 to 1,802) for severe frailty and 374 (187 to 4,484) in 'fit' patients. For femur fracture, NNH estimates were similar for first and second-generation AP drugs owing to the similar adjusted RR estimates, being 384 (202 to 1,248) and 365 (234 to 681) respectively for fit patients and 182 (96 to 592) and 173 (111 to 323) respectively in severe frailty. Table 3 presents equivalent results for Charlson comorbidity category. These results show a similar pattern of association but there was generally lower separation between comorbidity categories than for frailty categories.

DISCUSSION

Exposure to AP drugs is strongly associated with increasing age, frailty category and dementia diagnosis. The study provides evidence that even after allowing for patients' frailty level, first-generation AP drugs may be associated with increased overall risk of fracture, with evidence of increased risk for fractures of the femur, pelvis and wrist and hand. Second-generation AP drug exposure was associated specifically with increased risk of femur fractures. The study did not find evidence that the relative rate of fracture associated with AP drugs varied systematically by frailty level. There was no evidence for an increasing trend in relative risk estimates as frailty progressed and overall tests for interaction provided either no evidence (first-generation AP) or only weak evidence (second-generation AP) of differential effect. However, the underlying absolute risk of fracture increased steeply with frailty level, as noted in a previous study.[17] Consequently, absolute risks from AP exposure are greater, with smaller 'numbers need to harm', as frailty level increases. In severe frailty, we estimate that one fracture at any site might result from 75 person-years of exposure to first-generation AP drugs, while one femur fracture might result from 173 person-years of exposure to second-generation AP drugs.

For comparison, we also evaluated comorbidity using the Charlson index. Patients with higher Charlson comorbidity categories were more likely to have advanced frailty but there was imperfect agreement between the two measures; this is expected because they include different items and employ different data definitions. We found evidence that the number needed to harm will generally be smaller for patients with more advanced Charlson comorbidity category than for those with no comorbidity. Frailty, comorbidity and multiple morbidity are closely related concepts that do not have universally agreed definitions. This comparison of data using the frailty index with the Charlson comorbidity index, suggests that our conclusions are likely to hold across different measures of severity and vulnerability, though measures that are tailored to an older age population may often be preferred.

We also noted that patients with a diagnosis of dementia are much more likely to be exposed to antipsychotic drug treatment and consequently to associated risks of AP-associated fracture. Further research is needed into fracture risk in dementia, ideally across multiple severity levels, to explore whether fracture risks are conveyed by important non-dementia factors including therapeutic interventions.

Comparison with other studies

Previous studies have evaluated antipsychotic drug use and risk of fracture but have not evaluated the implications of frailty for this association. In their systematic review of observational studies up to 2016, Lee et al.[10] found that first-generation AP were associated with fractures of the hip and femur with a pooled odds ratio of 1.67 (1.45 to 1.93), while second-generation AP were associated with a pooled odds ratio of 1.33 (1.11 to 1.58) for fractures at the same site. The review found that any use of AP was associated with fractures at any site (odds ratio 1.46, 1.31 to 1.64) but there was strong evidence of heterogeneity. The present result suggest that first-generation AP may be associated with fractures of the pelvis and wrist, in addition to femur fractures. Lee et al.[10] concluded that second-generation AP were not associated with fractures at any site but the estimate was imprecise (odds ratio 1.19, 0.85 to 1.68). In the present large cohort, second-generation AP were found to be associated with any fracture, but there was a stronger association with hip fracture only. Fraser et al.[25] reported the only previous study with a comparable sample size to the present work, drawing on administrative data in Canada for 195,554 patients. Their study found that utilisation of second-generation AP drugs was associated with hip fracture (odds ratios 1.67, 1.53 to 1.81) and any fracture (1.29, 1.24 to 1.34). Hip fracture accounted for less than one third of fractures in both the Canadian study and our own.[25] Previous studies are consistent in associating either first- or second-generation AP drug use with hip fracture, while association with any fracture is stronger for first-generation AP drugs but still present for second-generation drugs.

306 *Strengths and limitations*

307 The study benefited from a large representative sample from a well-established and well-
308 validated national data resource.[18] The study drew on data for prescriptions issued in
309 primary care. It is possible that some patients might be exposed to AP drugs if they were
310 admitted to hospitals. Prescriptions issued by out-of-hours providers might also not be
311 recorded. The effect of this misclassification may be to diminish estimated associations. The
312 importance of this effect is difficult to determine but Stocks et al.[9] found a high proportion of
313 patients with dementia were prescribed AP in community settings and this probably
314 represents the largest group of indications at population level. Fractures were ascertained
315 from primary care records and we did not have access to linked hospital episodes data.
316 However, we believe it is unlikely that an older person will have a fracture without this event
317 being recorded by their family physician. We evaluated frailty using an established frailty
318 measure that is grounded in the deficit accumulation model.[15] Data from electronic records
319 were used to estimate frailty level but misclassification might occur if deficits were present
320 but not yet documented in medical records. It is important to be aware that frailty is a clinical
321 syndrome and the wide range of available measurement tools may offer different levels of
322 prediction for different health outcomes.[26] While the frailty index has mostly been validated
323 for prediction of mortality, measures of vulnerability to fracture might be considered for future
324 studies. In the initial validation study, c-statistic values close to 0.7 for mortality and
325 hospitalisation indicate moderate discrimination between patients who will or will not
326 experience these outcomes.[15] Furthermore, there are different models of frailty and the frailty
327 phenotype and frailty index have been contrasted in several studies,[27] but Zhu et al.[28] found
328 that both the frailty phenotype and frailty index were both associated with risk of falls in older
329 adults. We adjusted for the number of deficits present as well as frailty category and this
330 allowed adjustment for counts of a wide range of comorbidities. Our calculations of numbers
331 needed to treat, assume a causal association between AP use and fracture. This
332 assumption is supported by a previous systematic review of observational studies. However,

residual confounding by indication might cause bias because, as the present data show, patients who are more likely to have fractures are also more likely to be prescribed AP drugs. We estimated numbers needed to treat, assuming a common adjusted rate ratio for all patients. This was justified by the lack of strong evidence for effect modification and because estimates for sub-groups were imprecise. However, in an even larger study frailty category-specific relative risk estimates might be used.

Conclusions and Implications

In a population of older adults, AP prescription in primary care is associated with advancing age, frailty level and a dementia diagnosis. Both first- and second-generation AP drugs may be associated with increased risk of femur fractures; there is also evidence for increased risk of fragility fractures at other sites, though the risk is greater for first-generation AP drugs. The absolute risk of an AP-associated fracture is greatest, and the number needed to harm is lowest, in patients with severe frailty who are more likely to be prescribed AP drugs. While older guidance on AP prescribing suggests that risks of mortality and stroke should be important concerns, the present study adds to more recent evidence that affirms the risk of falls and factures during AP utilisation. Consequently, fracture risk and frailty level should be considered in the context of decision-making with respect to antipsychotic prescribing in older adults.

REFERENCES

1. Hazra NC, Gulliford M. Evolution of the "fourth stage" of epidemiologic transition in people aged 80 years and over: population-based cohort study using electronic health records. *Population Health Metrics* 2017;**15**:10. doi: 10.1186/s12963-017-0136-2

2. Hazra NC, Rudisill C, Gulliford MC. Determinants of health care costs in the senior elderly: age, comorbidity, impairment, or proximity to death? *Eur J Health Econ* 2018; **19:**831-842 doi: 10.1007/s10198-017-0926-2

3. All-Party Parliamentary Group on Dementia. *Prepared to care. Challenging the dementia skills gap.* London: All-Party Parliamentary Group on Dementia, 2009. Source: https://www.alzheimers.org.uk/sites/default/files/migrate/downloads/appg_report_prepared_to_care.pdf accessed 8th October 2018.

4. Parnetti L, Amici S, Lanari A, et al. Pharmacological treatment of non-cognitive disturbances in dementia disorders. *Mech Ageing Dev* 2001;**122**:2063-69. doi: 10.1016/s0047-6374(01)00316-5

5. Travers C, Byrne GJ, Pachana NA, et al. Delirium in Australian hospitals: a prospective study. *Cur gerontol geriatr res* 2013;**2013**:284780. doi: 10.1155/2013/284780

6. Lee PE, Gill SS, Freedman M, et al. Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review. *BMJ* 2004;**329**:75. doi: 10.1136/bmj.38125.465579.55

7. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psych* 2006;**14**:191-210. doi: 10.1097/01.JGP.0000200589.01396.6d

8. Banerjee S. *The use of antipsychotic medication for people with dementia: time for action. A report for the Minister of State for Care Services.* London: Department of Health 2009. Source: https://www.rcpsych.ac.uk/pdf/Antipsychotic%20Bannerjee%20Report.pdf accessed 8th October 2018.

9. Stocks SJ, Kontopantelis E, Webb RT, et al. Antipsychotic Prescribing to Patients Diagnosed with Dementia Without a Diagnosis of Psychosis in the Context of National Guidance and Drug Safety Warnings: Longitudinal Study in UK General Practice. *Drug safety* 2017;**40**:679-92. doi: 10.1007/s40264-017-0538-x

10. Lee S-H, Hsu W-T, Lai C-C, et al. Use of antipsychotics increases the risk of fracture: a systematic review and meta-analysis. *Osteoporosis International* 2017;**28**:1167-78. doi: 10.1007/s00198-016-3881-3

11. Gulliford M, Ravindrarajah R. Frailty: from clinical syndrome to epidemiological construct? *The Lancet Public Health* 2018;**3**:e305-e06. doi: https://doi.org/10.1016/S2468-2667(18)30112-9

12. Fried LP, Tangen CM, Walston J, et al. Frailty in Older Adults: Evidence for a Phenotype. *J Gerontol Series A: Biol Sci Med Sci* 2001;**56**:M146-M57. doi: 10.1093/gerona/56.3.M146

13. Rockwood K, Mitnitski A. Frailty in Relation to the Accumulation of Deficits. *J Gerontol Series A: Biol Sci Med Sci* 2007;**62**:722-27. doi: 10.1093/gerona/62.7.722

14. Hanlon P, Nicholl BI, Jani BD, et al. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of UK Biobank participants. *The Lancet Public Health* 2018;**3**:e323-e32. doi: 10.1016/S2468-2667(18)30091-4

15. Clegg A, Bates C, Young J, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age and Ageing* 2016;**45**:353-60. doi: 10.1093/ageing/afw039

16. Ravindrarajah R, Hazra NC, Hamada S, et al. Systolic Blood Pressure Trajectory, Frailty and All-Cause Mortality Over 80 Years of Age. Cohort Study Using Electronic Health Records. *Circulation* 2017;**135**:2357-2368. doi: 10.1161/circulationaha.116.026687

17. Ravindrarajah R, Hazra NC, Charlton J, et al. Incidence and mortality of fractures by frailty level over 80 years of age: cohort study using UK electronic health records. *BMJ open* 2018;**8;** e018836. doi: 10.1136/bmjopen-2017-018836

18. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;**44**:827-36. doi: 10.1093/ije/dyv098

19. Nicholas JM, Ridsdale L, Richardson MP, et al. Fracture risk with use of liver enzyme inducing antiepileptic drugs in people with active epilepsy: Cohort study using the General Practice Research Database. *Seizure* 2013;**22**:37-42. doi: 10.1016/j.seizure.2012.10.002

20. Torstensson M, Hansen AH, Leth-Møller K, et al. Danish register-based study on the association between specific cardiovascular drugs and fragility fractures. *BMJ open* 2015;**5**:e009522. doi: 10.1136/bmjopen-2015-009522

21. Sporer SM, Weinstein JN, Koval KJ. The geographic incidence and treatment variation of common fractures of elderly patients. *J Am Acad Orthop Surg* 2006;**14**:246-55.

22. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987;**40**:373-83.

430 23. Khan NF, Perera R, Harper S, et al. Adaptation and validation of the Charlson Index for
431 Read/OXMIS coded databases. *BMC family practice* 2010;**11**:1. doi: 10.1186/1471-
432 2296-11-1 [published Online First: 2010/01/07]

433 24. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP, 2015.

434 25. Fraser L, Liu K, Naylor KL, et al. Falls and fractures with atypical antipsychotic
435 medication use: A population-based cohort study. *JAMA Intern Med* 2015;**175**:450-
436 52. doi: 10.1001/jamainternmed.2014.6930

437 26. . Dent E, Kowal P, Hoogendijk EO. Frailty measurement in research and clinical practice:
438 A review. *Eur J Int Med* 2016;**31**:3-10. doi: https://doi.org/10.1016/j.ejim.2016.03.007

439 27. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype.
440 *J Gerontol Series A Biol Sci Med Sci* 2001;**56**; M146-7. doi:
441 10.1093/gerona/56.3.M146

442 28. Zhu Y, Liu Z, Wang Y, et al. Agreement between the frailty index and phenotype and
443 their associations with falls and overnight hospitalizations. Arch Gerontol Geriatr
444 2016;**66**:161-65. doi: https://doi.org/10.1016/j.archger.2016.06.004

445

446

447

448

449

Table 1: Baseline characteristics of patients who received no AP prescriptions, or one or more first- or second-generation AP prescriptions. Figures are frequencies (column percent) except where indicated.

		No AP	First-generation AP			Second-generation AP		
		Freq. (%)	Freq. (%)	Relative odds of 1st generation AP treatment (95% CI)[a]	P value	Freq. (%)	Relative odds of 2nd generation AP treatment (95% CI)[a]	P value
Total[b]		143,406	4,078			5,856		
Gender	Male	56,189 (39)	1,513 (37)	-		1,677 (29)	-	
	Female	87,217 (61)	2,565 (63)	0.87 (0.81 to 0.93)	<0.001	4,179 (71)	1.14 (1.07 to 1.21)	<0.001
Age-group (Years)	80-84	105,270 (73)	1,641 (40)	-		2,637 (45)	-	
	85-89	22,873 (16)	1,288 (32)	3.20 (2.96 to 3.46)	<0.001	1,842 (31)	2.34 (2.19 to 2.50)	<0.001
	90-94	11,065 (8)	809 (20)	3.76 (3.43 to 4.12)	<0.001	1,010 (17)	2.34 (2.15 to 2.54)	<0.001
	95-99	3,428 (2)	277 (7)	4.67 (4.06 to 5.38)	<0.001	318 (5)	2.63 (2.30 to 3.01)	<0.001
	100+	770 (1)	63 (2)	6.95 (5.31 to 9.08)	<0.001	49 (1)	2.78 (2.01 to 3.84)	<0.001
Frailty	Fit	50,905 (36)	530 (13)	-		1,029 (18)	-	
	Mild	58,480 (41)	1,500 (37)	1.76 (1.58 to 1.97)	<0.001	2,422 (41)	1.57 (1.44 to 1.70)	<0.001
	Moderate	26,913 (19)	1,327 (33)	2.87 (2.55 to 3.22)	<0.001	1,692 (29)	2.20 (2.00 to 2.42)	<0.001
	Severe	7,108 (5)	721 (18)	5.55 (4.83 to 6.36)	<0.001	713 (12)	3.50 (3.10 to 3.95)	<0.001
Long-term conditions	Cancer	39,363 (27)	1,627 (40)	1.45 (1.35 to 1.55)	<0.001	1,214 (21)	0.70 (0.65 to 0.75)	<0.001
	IHD	33,190 (23)	1,041 (26)	0.71 (0.66 to 0.77)	<0.001	1,245 (21)	0.72 (0.67 to 0.78)	<0.001
	Dementia	20,683 (14)	1,604 (39)	2.68 (2.50 to 2.88)	<0.001	3,718 (63)	7.64 (7.21 to 8.09)	<0.001
	Diabetes	26,099 (18)	726 (18)	0.63 (0.60 to 0.70)	<0.001	947 (16)	0.73 (0.67 to 0.79)	<0.001
	Stroke	15,718 (11)	649 (16)	0.92 (0.84 to 1.00)	0.061	826 (14)	0.90 (0.83 to 0.97)	0.010
Charlson Category	0	49,962 (35)	471 (12)	-	<0.001	1,012 (17)	-	<0.001
	1-2	56,019 (39)	1,631 (40)	2.02 (1.80 to 2.26)	<0.001	2,702 (46)	1.43 (1.32 to 1.56)	<0.001
	3-4	27,512 (19)	1,214 (30)	2.50 (2.20 to 2.83)	<0.001	1,553 (27)	1.59 (1.44 to 1.75)	<0.001
	≥5	9,903 (7)	762 (19)	4.03 (3.48 to 4.68)	<0.001	589 (10)	1.79 (1.57 to 2.05)	<0.001

CI, confidence interval; OR, odds ratio. [a]odds ratios were adjusted for each of the variables shown. [b]36 patients were prescribed both first- and second-generation AP drugs in separate treatment episodes

Table 2: Estimates for 'number needed to harm' by frailty category.

Frailty category	Fracture incidence (per 1,000)	First-generation AP		Second-generation AP	
		Rate ratio (95% CI)[a]	'Number needed to harm'[a]	Rate ratio (95% CI)[a]	'Number needed to harm'[a]
ANY FRACTURE					
		1.24 (1.07 to 1.43)		1.12 (1.01 to 1.24)	
Fit	22.3		187 (104 to 641)		374 (187 to 4,484)
Mild frailty	32.9		127 (71 to 434)		253 (127 to 3,040)
Moderate frailty	42.3		99 (55 to 338)		197 (99 to 2,364)
Severe frailty	55.5		75 (42 to 257)		150 (75 to 1,802)
FEMUR FRACTURE					
		1.39 (1.12 to 1.74)		1.41 (1.22 to 1.64)	
Fit	6.67		384 (202 to 1,248)		365 (234 to 681)
Mild frailty	9.83		261 (137 to 847)		248 (159 to 462)
Moderate frailty	12.51		205 (108 to 666)		195 (125 to 363)
Severe frailty	14.09		182 (96 to 592)		173 (111 to 323)

[a] Rate ratios (RR) were adjusted for age, age-squared, gender, dementia, frailty category, number of deficits and clustering by patient.
[b]number needed to harm – the number of patients required to be treated for one year to produce one additional fracture
AP, antipsychotic; CI, confidence interval

Table 3: Estimates for 'number needed to harm' by Charlson comorbidity category.

Charlson category	Fracture incidence (per 1,000)	First-generation AP		Second-generation AP	
		Rate ratio (95% CI)[a]	'Number needed to harm'[a]	Rate ratio (95% CI)[a]	'Number needed to harm'[a]
ANY FRACTURE					
		1.37 (1.18 to 1.58)		1.19 (1.08 to 1.32)	
0	26.3		103 (66 to 212)		200 (119 to 476)
1-2	33.6		80 (51 to 165)		157 (93 to 372)
3-4	34.3		79 (50 to 162)		153 (91 to 364)
≥5	36.4		74 (47 to 153)		145 (86 to 343)
FEMUR FRACTURE					
		1.49 (1.19 to 1.86)		1.47 (1.27 to 1.71)	
0	7.59		269 (153 to 693)		280 (185 to 488)
1-2	9.98		204 (117 to 527)		213 (141 to 371)
3-4	10.2		199 (114 to 514)		208 (138 to 362)
≥5	11.0		186 (106 to 478)		193 (128 to 337)

[a] Rate ratios (RR) were adjusted for age, age-squared, gender, dementia, Charlson category and clustering by patient.
[b]number needed to harm – the number of patients required to be treated for one year to produce one additional fracture
AP, antipsychotic; CI, confidence interval

Legend for Figure 1:

Figure 1: Exposure to first- and second-generation antipsychotic drugs by levels of covariates. Figures are number of patients ever exposed, adjusted odds ratio (95% confidence interval) compared with reference category for each variable, adjusted for each of the variables shown as well as cancer, ischaemic heart disease, diabetes and stroke.

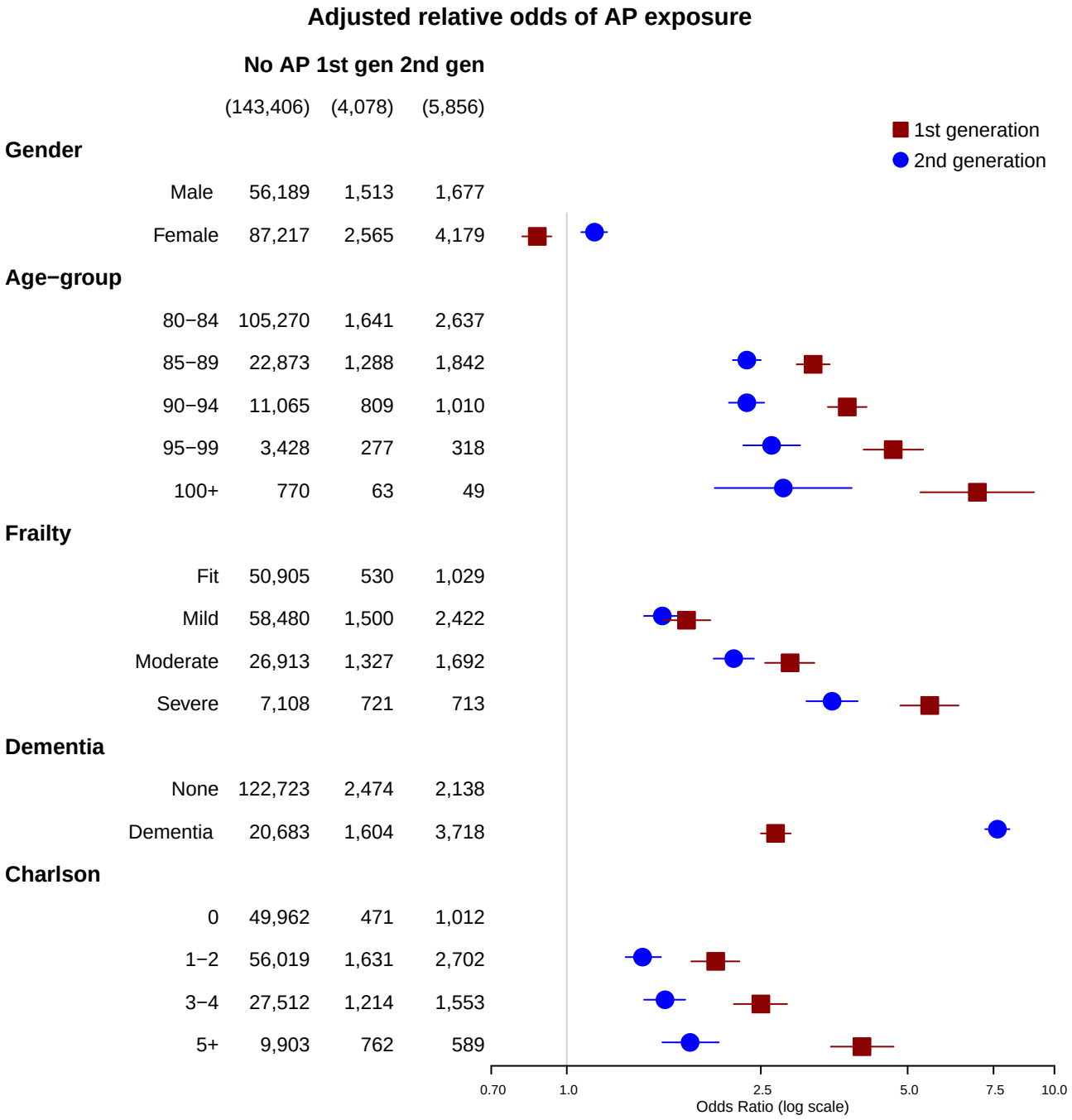
Legend for Figure 2:

Figure 2: Fracture rate by AP exposure and fracture site. Figures are frequencies except where indicated. Rate ratios (RR) were adjusted for age, age-squared, gender, dementia, frailty category, number of deficits and clustering by patient. CI, confidence interval; RR, rate ratio.

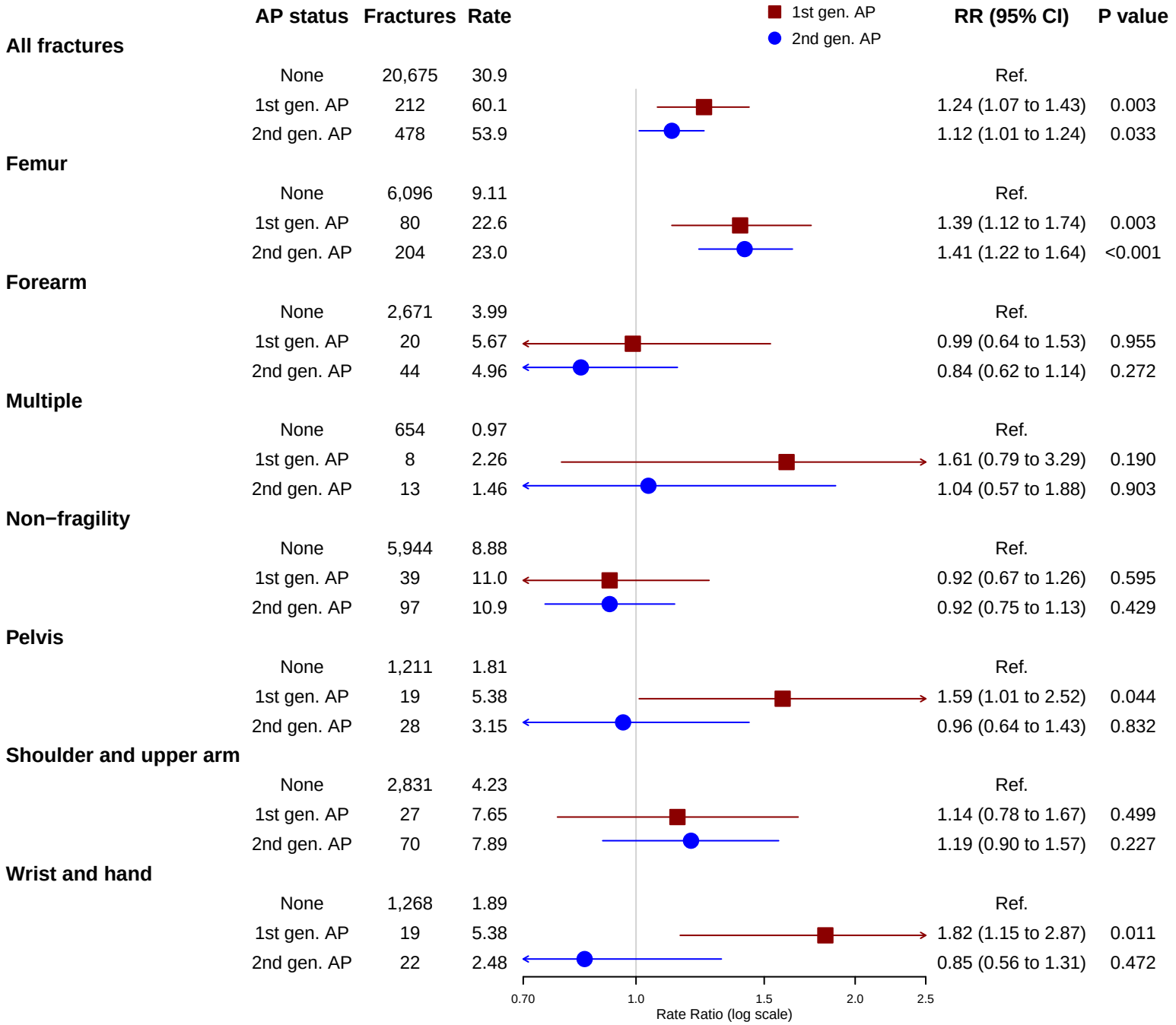
Supplementary Material

Click here to download Supplementary Material: APFractures7May2019CleanCopy.docx

Figure


Adjusted relative odds of AP exposure
No AP 1st gen 2nd gen
(143,406) (4,078) (5,856)
1st generation
2nd generation
Gender
Male 56,189 1,513 1,677
Female 87,217 2,565 4,179
Age−group
80−84 105,270 1,641 2,637
85−89 22,873 1,288 1,842
90−94 11,065 809 1,010
95−99 3,428 277 318
100+ 770 63 49
Frailty
Fit 50,905 530 1,029
Mild 58,480 1,500 2,422
Moderate 26,913 1,327 1,692
Severe 7,108 721 713
Dementia
None 122,723 2,474 2,138
Dementia 20,683 1,604 3,718
Charlson
0 49,962 471 1,012
1−2 56,019 1,631 2,702
3−4 27,512 1,214 1,553
5+ 9,903 762 589
0.70
1.0
2.5
5.0
7.5
10.0
Odds Ratio (log scale)

Figure


AP status
Fractures
Rate
1st gen. AP
2nd gen. AP
RR (95% CI)
P value
All fractures
None 20,675 30.9 Ref.
1st gen. AP 212 60.1 1.24 (1.07 to 1.43) 0.003
2nd gen. AP 478 53.9 1.12 (1.01 to 1.24) 0.033
Femur
None 6,096 9.11 Ref.
1st gen. AP 80 22.6 1.39 (1.12 to 1.74) 0.003
2nd gen. AP 204 23.0 1.41 (1.22 to 1.64) <0.001
Forearm
None 2,671 3.99 Ref.
1st gen. AP 20 5.67 0.99 (0.64 to 1.53) 0.955
2nd gen. AP 44 4.96 0.84 (0.62 to 1.14) 0.272
Multiple
None 654 0.97 Ref.
1st gen. AP 8 2.26 1.61 (0.79 to 3.29) 0.190
2nd gen. AP 13 1.46 1.04 (0.57 to 1.88) 0.903
Non−fragility
None 5,944 8.88 Ref.
1st gen. AP 39 11.0 0.92 (0.67 to 1.26) 0.595
2nd gen. AP 97 10.9 0.92 (0.75 to 1.13) 0.429
Pelvis
None 1,211 1.81 Ref.
1st gen. AP 19 5.38 1.59 (1.01 to 2.52) 0.044
2nd gen. AP 28 3.15 0.96 (0.64 to 1.43) 0.832
Shoulder and upper arm
None 2,831 4.23 Ref.
1st gen. AP 27 7.65 1.14 (0.78 to 1.67) 0.499
2nd gen. AP 70 7.89 1.19 (0.90 to 1.57) 0.227
Wrist and hand
None 1,268 1.89 Ref.
1st gen. AP 19 5.38 1.82 (1.15 to 2.87) 0.011
2nd gen. AP 22 2.48 0.85 (0.56 to 1.31) 0.472
0.70
1.0
1.5
2.0
2.5
Rate Ratio (log scale)

Supplementary Material

Click here to download Supplementary Material: JAMDA-D-19-0288SupplementaryTables.docx

Letter

Click here to download Letter: GafoorCoveringLetter9April2019.docx

Faculty of Life Sciences

& Medicine

School of Population Sciences & Health Services Research

Professor Charles Wolfe
MD FFPH FRCOG
Head of School

Addison House
Guy's Campus
King's College London
SE1 1UL
Tel 020 7848 6643/6604/6649
Fax 020 7848 6620
hscr@kcl.ac.uk
www.kcl.ac.uk/HSCR
www.twitter.com/KCL_HSCR

Dr Philip D. Sloane, MD, MPH

Editor-in-Chief,

Journal of the American Medical Directors Association

9th April 2019

Dear Dr Sloane

JAMDA-D-19-00288: Importance of frailty for association of antipsychotic drug use with risk of fracture. Cohort study using electronic health records

Thank you for your communication dated 6th April 2019. We are very appreciative of the very timely response of the reviewer and editor to our submission.

Thank you also for sending the reviewer's comments on our paper. We agree that these raise some important issues that needed addressing. We have now revised the paper and have addressed each of the reviewer comments. Our point-by-point response is given in a separate document. We have also highlighted changes in the manuscript.

Addition of this material has increased the word count to 3,781 words. However, we have only cited 28 references. If required, we would be prepared to transfer some of this material to a supplementary file.

Thank you for considering our revised paper for possible publication in the *Journal of the American Medical Directors Association.*

With best wishes

Yours sincerely

Martin Gulliford MA FRCP FFPH

Professor of Public Health

JAMDA-D-19-00288 Response to reviewer comments

Valuable large data-base study.

Thank you for this feedback.

The biggest question is whether and to what extent what you measured is frailty, frailty risk, or comorbidity.

Thank you for this comment, we agree this is a relevant concern. We have now addressed the reviewer's detailed comments as outlined below.

1. The frailty measure used in this study has several potential drawbacks. Please address these in a revision:

(a) It is a relatively new measure and as such requires evidence of validation. Please provide this in a paragraph, with citations, in the methods section.

Thank you for this important point. We now discuss the concept of frailty in the Introduction section (pages 3-4) where it now reads: 'In recent years, there have been advances in the understanding and measurement of age-related frailty as a condition of heightened vulnerability in older people. The frailty concept has no unique definition and can be measured using several different tools.[11] The frailty phenotype draws on the co-occurrence of several non-specific clinical features including weakness, fatigue, weight loss, inactivity and slow walking speed.[12] The frailty index approach evaluates the number of deficits, which may include symptoms, signs, diseases or laboratory measurements.[13] Frailty shows considerable overlap with the concepts of comorbidity and multiple morbidity. In UK Biobank data, people with four or more long term conditions had 27 times higher odds of the frailty phenotype.[14] For the present study we employed the e-Frailty Index (eFI)[15] because this is readily operationalised into electronic health records.[16] The eFI evaluates the presence of 36 deficits as a proportion of the total possible, leading to a categorisation of 'fit', 'mild', 'moderate' or 'severe' frailty.[15] As evidence of validity, increasing frailty level using the eFI is strongly associated with mortality, hospitalisation or nursing home admission.[15] Frailty status is also associated with the incidence of fragility and non-fragility fractures.[17,

(b) In your validation, if possible, compare your index with a frailty syndrome measure. As you know, there are two general groups of frailty researchers, the Rockwood / deficit accumulation group and the Fried / frailty syndrome group. The index you used is of the former type and as such as appropriate for large data base studies such as yours; however, cross-validation with a Fried-type measure would strengthen its acceptability.

Thank you we now address this point in the Discussion section (page 12) where we now say: 'It is important to be aware that frailty is a clinical syndrome and the wide range of available measurement tools may offer different levels of prediction for different health

outcomes. While the frailty index has mostly been validated for prediction of mortality, measures of vulnerability to fracture might be considered for future studies… Furthermore, there are different models of frailty and the frailty phenotype and frailty index have been contrasted in several studies, but Zhu et al. found that both the frailty phenotype and frailty index were both associated with risk of falls in older adults.'

(c) The degree and quality of validation studies should be discussed under potential limitations.

Thank you, we now add (page 12): 'In the initial validation study, c-statistic values close to 0.7 for mortality and hospitalisation indicate moderate discrimination between patients who will or will not experience these outcomes.[15]'

2. Consider adding the Charlson Comorbidity index as a variable to your analyses. This would help provide cross-validation of the frailty measure and introduce a more widely-accepted measure to your adjustment.

Thank you for this suggestion. We now add:

Introduction (page 4): 'We also compared estimates with those obtained using the Charlson comorbidity index for risk stratification.'

Methods (page 6): 'At the peer-review stage, we added the Charlson Comorbidity index[22] in order to introduce a more widely-accepted measure as a variable to provide cross-validation of the frailty measure. The Charlson score was evaluated as reported by Khan et al.[23] The Charlson index was analysed using the categories of zero, 1-2, 3-4 and ≥5, as suggested by Charlson et al.[22]'

Results (pages 8-9): 'Prescription of antipsychotic drugs was associated with Charlson comorbidity category but associations were slightly less strong than for frailty category. Supplementary Table 1 presents a cross-tabulation of the frailty and comorbidity indices, showing strong association between the two metrics. Patients with a Charlson comorbidity category of five or greater had 73.1 (95% confidence interval 63.9 to 83.6) times higher odds of severe frailty than patients with a Charlson comorbidity category of zero.'

(Please note that the estimates in Table 1 have now changed owing to additional adjustment for the Charlson index.)

Results (page 10): ‘Table 3 presents equivalent results for Charlson comorbidity category. These results show a similar pattern of association but there was generally lower separation between comorbidity categories than for frailty categories.’

Discussion (page 11): ‘For comparison, we also evaluated comorbidity using the Charlson index. Patients with higher Charlson comorbidity categories were more likely to have advanced frailty but there was imperfect agreement between the two measures; this is expected because they include different items and employ different data definitions. We found evidence that the number needed to harm will generally be smaller for patients with more advanced Charlson comorbidity category than for those with no comorbidity. Frailty, comorbidity and multiple morbidity are closely related concepts that do not have universally agreed definitions. This comparison of data using the frailty index with the Charlson comorbidity index, suggests that our conclusions are likely to hold across different measures of severity and vulnerability, though measures that are tailored to an older age population may often be preferred.’

3. More data and discussion should be provided to the association observed between dementia and fracture risk. In particular the data presented should help the reader understand whether dementia (ideally as multiple severity levels) is a stronger risk factor for fracture, or whether the risk is conveyed by non-dementia factors. This would be a clinically important point to tease out.

Thank you for this comment. We are concerned that are labelling of Table 1 might have contributed to mis-understanding. The odds ratios in Table 1 show the odds of receiving AP treatment for different groups of patients Therefore, we have improved the clarity to read ‘Relative odds of 1st generation AP treatment (95% CI).’

We also comment in the Discussion (page 11): ‘We also noted that patients with a diagnosis of dementia are much more likely to be exposed to antipsychotic drug treatment and consequently to associated risks of AP-associated fracture. Further research is needed into fracture risk in dementia, ideally across multiple severity levels, to explore whether fracture risks are conveyed by important non-dementia factors including therapeutic interventions.’

We suggest that in-depth study of fracture risk in dementia patients should be done in a study designed for that purpose, rather than as a sub-group analysis of this study of a general population sample.