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| Host department:Keele |
| Project Title: |
| Ageing well with pain: identifying the group of oldest old population most at risk of poor outcomes |
| Proposed supervisory team:  |
| Dr Milica Bucknall (Keele. Lead-supervisor; extensive experience as lead statistician in treatment-outcome research using medical records). Dr Victoria Welsh (Keele. Joint lead supervisor; expertise in clinical practice and medical records research, joint PI on SNIPE and SPLaT-19)Dr Li-Chia Chen (Manchester. Co-supervisor. Expertise in pharmacy, extensive experience with medical records research and opioid prescription data)Dr Claire Burton (Keele. Co-supervisor; expertise in clinical practice and medical records research, joint PI on SNIPE and SPLaT-19)Dr Kayleigh Mason (Keele. Co-supervisor; expertise in pharmacoepidemiology, cohort studies in primary and secondary care, and is the lead analyst for 2 CPRD studies (MSKCOM; SNIPE)). All supervisors have experience of supervising PhD students.  |
| Potential for cross consortium networking and educational opportunities: |
| There is potential to build upon existing relationships between Keele and leading institutions active in opioids, frailty and pain research including Professors Ashcroft (Manchester), Gladman (Nottingham), and Walsh (Nottingham) within the consortium and Forster (Leeds), Clegg (Bradford), and Schofield (Plymouth) additionally. International collaboration with Professor Suzanne Levielle (Harvard, USA) is possible. The proposed PhD offers the opportunity to obtain practical experience in using routinely collected electronic health records including handling and manipulation of big-data, statistical analysis software use, and application of different analysis techniques.  |
| Project description: |
| Research question: Can a distinct cluster(s) of the oldest old population who are at greatest risk of adverse events associated with analgesic prescribing be identified? Background: Pain is a common experience amongst older adults; 63% of adults aged 85 years and older report experiencing joint pain in the last month. Pain is associated with the subsequent development and progression of frailty, falls and future limitation of activities of daily living and physical performance.1,2,3,4 Pain becomes increasingly complex to manage with advancing age due to the development of multimorbidity, polypharmacy and frailty syndrome. Guidelines recommend non-pharmacological strategies including physiotherapy and exercise,5 though these can be difficult to access for the oldest old due to physical immobility and social isolation. Thus, often, the prescribing of analgesia forms a significant part of pain management for this group. Our public advisory group described how there is variation between doctors and their advice regarding the prescribing of analgesic medication. These differences occur because, although there are known generic side effects, this evidence is not derived from studies that include the oldest old population. Our public advisory group, local doctors and pharmacists have called for research to help clinicians, patients and their families better understand the harms associated with analgesics to enable informed decisions to be taken. There is a myriad of research relating to trends of opioid prescribing in primary care,6,7 and less so for non-opioid analgesics (for example paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids).8,9,10 However, to our knowledge, there are no published studies, or work in progress from recently published groups, that are investigating whether patients can be grouped into distinct clusters to identify those most at risk from associated adverse events. This study seeks to address this knowledge gap, providing evidence for clinicians, patients and their families to use in their discussions about analgesic prescribing in primary care consultations. The proposed PhD offers a different and complementary slant on the current work in area of aging well with pain, which predominantly focuses on the organisation of pain management services for those living with frailty, and non-pharmacological interventions.Objectives: The overall aim of the project is to identify a distinct cluster(s) of the oldest old population who are at the greatest risk of adverse events associated with analgesic prescribing. Specific objectives are to: 1. Undertake a scoping review to summarise the current evidence regarding adverse events associated with analgesic prescribing in the oldest old populations;
2. Assess whether the oldest old population can be grouped into distinct clusters based on their sociodemographic, lifestyle, comorbidity and frailty characteristics;
3. Compare patient characteristics between clusters;
4. Compare clusters in terms of risks of adverse events associated with analgesic prescribing;
5. Identify the group of oldest old population who are most at risk of poor outcomes.

Methods: The scoping review will be undertaken with support from the School of Medicine Systematic Review Team. *Data source/study population:* The project will use Clinical Practice Research Datalink (CPRD), a database of anonymized routinely collected primary care medical records, which covers over 7% of the UK population and is shown to be representative of the general UK population. Study population will consist of those with an opioid prescription at any point after 1/1/2009 but without such a prescription at least 12 months beforehand. 12 months is adequate to enable capture of exposure as incident opioid prescribing rather than continuance of an ongoing medication. The date of this incident opioid prescription will be defined as baseline, with patients aged ≥80 years on that date. Latest follow-up end point will be 31/06/2022. *Opioids:*  Analgesic medications will be grouped according to previously published work11 with additional categories added to take account of current clinical guidelines.12 Groups will cover paracetamol, NSAIDs, opioids, gabapentinoids, amitriptyline, anti-depressant medications licensed for pain. *Patient characteristics:* Demographics, lifestyle factors, polypharmacy, a wide range of comorbidities and information needed to calculate electronic frailty index (eFI).13 *Outcomes:* Our patient advisory group advised outcomes that impact upon the ability to live independently. These will include incidence of and time to: all-cause mortality, all-cause hospitalization, fragility fracture, falls, cognitive impairment (acute confusion, delirium, incident dementia), infection (pneumonia, lower respiratory tract infection, urinary tract infection, cellulitis), cardiovascular events, development/ progression of frailty, cancer, addiction, overdose and gastrointestinal events. *Analysis:* Analysis dataset will have to be derived from raw CPRD datasets, which will provide invaluable experience in handling and managing large electronic health record datasets. Descriptive statistics of the study sample will be obtained. Clustering of sociodemographic, lifestyle, comorbidity and frailty characteristics at baseline will be examined, to establish underlying factor structure among these characteristics. Principal components analysis will be performed to extract factors using various forms of rotation (e.g. oblique, orthogonal). Subsequently, hierarchical cluster analysis will be performed to place patients into homogeneous groups based on combinations of their characteristics, considering the same set as in the factor analysis. Identified clusters will then be compared with regards to specified outcomes above, using logistic and Cox regression models. Subgroup analyses will be performed by gender and by baseline eFI category. Sensitivity analyses to missing data and omission of cancer-related pain prescribing will also be undertaken. Timeline: Year 1: Data acquisition, derivation of analysis dataset, scoping literature review; Year 2: Main data analyses; Year 3: Subgroup and sensitivity analyses, finalising thesis write-up. Wider engagement, Patient and Public Involvement and Engagement, Outputs: The PhD will have a dedicated PPIE group who will advise on all aspects of the study including methodology, key findings and dissemination. A stakeholder group including members of the oldest old population living with pain and their families and carers, voluntary organisations, and health and social care professionals, will guide the PhD with an initial event at the beginning of the study period and an event at the end where key findings are disseminated, interpreted, and placed into context. Alongside publication in peer-reviewed journals and conference presentations, results will be shared using novel approaches in conjunction with the Keele Impact Accelerator Unit to ensure far-reaching dissemination that will empower patients and their families, and inform clinicians to enable effective evidence-based decision making over analgesic prescribing in primary care.  |
| Training and development provision by host: |
| *Formal training:* The student will be expected to undertake formal training to enable independent post-doctoral research development. This will include an introductory course to using electronic health records (e.g., Answering Clinical Research Questions with Health Records, UCL) and a course covering cluster analysis (e.g., Introduction to Cluster Analysis course, Manchester). The student will be expected to make use of the freely available training resources to enable confidence with independent statistical software use (e.g., STATA online courses). The Keele Systematic Review run workshops which the student is free to attend; their online lecture series will also be available to view.  |
| *Informal training:* The supervisory team will formally meet monthly with the student to discuss any issues, training needs, progress, agree timelines and provide feedback. Informal meetings with any of the supervisors will take place when needed. The student will be encouraged to begin thesis planning and writing from the project outset. The student will have opportunities to teach elementary epidemiological concepts to undergraduate medical students. The student will be part of the Musculoskeletal Health Faculty Research Theme and can access resources through this including mentor support and research guidance. Membership to the Medical Records Research team will be provided to enable wider engagement with our health-data researchers. The student will be encouraged to present their work at the Keele Postgraduate Symposium alongside national conferences (e.g., Society of Academic Primary Care).  |
| *PPIE:* The student will work closely with the Keele PPIE group at key stages: project outset, mid-project and project end. PPIE group will guide study design, analysis and results dissemination. Presentation at local and national PPIE engagement events will be encouraged. The PPIE work will be guided by the principles set out in the UK Standards for Public Involvement. 14 |

**References:**

1.Duncan R et al. Prevalence of arthritis and joint pain in the oldest old: findings from the Newcastle 85+ study. Age Ageing 2011 Nov;40(6):752-755.

2. Wade KF et al. Does Pain Predict Frailty in Older Men and Women? Findings From the English Longitudinal Study of Ageing (ELSA). J Gerontol A Biol Sci Med Sci 2017 Mar 1;72(3):403-409.

3. Welsh VK et al. Investigating multisite pain as a predictor of self-reported falls and falls requiring health care use in an older population: A prospective cohort study. PLoS One 2019;14(12):e0226268.

4. Yiengprugsawan V et al. Prospective analyses of pain and physical functioning in the English Longitudinal Study of Ageing. Innovation in Aging 2017;1:593-594.

5. National Institute for Health and Care Excellence Osteoarthritis: care and management. Updated 11 Dec 2020.

6. Jani M et al. Time trends and prescribing patterns of opioid drugs in UK primary care patients with non-cancer pain: A retrospective cohort study. PLoS Med. 2020 Oct 15;17(10):e1003270.

7. Davies E et al. Examining opioid prescribing trends for non-cancer pain using an estimated oral morphine equivalence measure: a retrospective cohort study between 2005 and 2015. BJGP Open. 2021 23;5(1):bjgpopen20X101122.

8. Conaghan PG et al. Safety of Paracetamol in Osteoarthritis: What Does the Literature Say? Drugs Aging. 2019 Apr;36(Suppl 1):7-14.

9. Woo SD et al. Common causes and characteristics of adverse drug reactions in older adults: a retrospective study. BMC Pharmacol Toxicol. 2020 Dec 10;21(1):87.

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11. Bedson et al. The effectiveness of national guidance in changing analgesic prescribing in primary care from 2002 to 2009: an observational database study. Eur j Pain. 2013 17(3):434-43.

12. Welsh VK et al. Musculoskeletal pain during the COVID-19 pandemic: an observational study of UK national primary care electronic health records (the SNIPE Study).2020.

13. Clegg A et al.Development and validation of an electronic frailty index using routine primary care electronic health record data. Age and Ageing 2016; 45 (3):353-360. 14. National Institute for Health and Care Excellence et al. UK Standards for Public Involvement. Nov 2019.