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Development of the AC-FRAIL tool: A case-finding tool to identify anticholinergic burden amongst older people living with frailty.

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Key points

- The AC-FRAIL tool proactively case-finds older people within a practice population, likely to be living with frailty, and exposed to higher levels of anticholinergic burden.
- The cumulative effect of multiple anticholinergic medicines (with antimuscarinic properties) raises concerns within observational research, found to be associated with various severe adverse outcomes.
- Older people living with frailty are less likely to tolerate the adverse effects of anticholinergic medicines, and are more likely to experience adverse outcomes.
- As of writing, it is not possible to generate total anticholinergic burden scores within clinical systems for a practice population.
- In general, frailty is superior to age in identifying at-risk older people. The NHS are encouraging proactive approaches to medication reviews, with new policies recommending targeted reviews in the moderate-severely frail.
- The AC-FRAIL tool can assist practices with identifying older people at greatest risk from anticholinergic burden, to support with medicines optimisation and deprescribing interventions.

Introduction

Older people living with frailty exposed to polypharmacy are at higher risk of suffering adverse events [1]. The much-needed process of identifying patients for medication review tends to be reactive rather than planned, with few solutions capable of proactive identification using electronic health care records [2, 3]. This article describes the development of a case-finding tool, capable of identifying older people with frailty exposed to anticholinergics, and at greater risk of the adverse effects associated with anticholinergic burden.

Frailty: an important consideration when prescribing

Frailty is a clinical state associated with vulnerability to adverse health outcomes, such as falls, long-term care, disability and death [4], and is seen in an estimated quarter to half of over 85-year-olds [5, 6]. Age-related decline in function and physiologic reserves across multiple organ systems can lead to failure of homeostatic mechanisms, compromising one's ability to cope with stressors [4, 7]. Older people are considered to have greater susceptibility to the adverse effects of medicines, however in frailty this is thought to more pronounced, with greater implications for pharmacokinetics and pharmacodynamics [1]. Additional caution should be applied when managing pharmacotherapies in frailty; a condition considered to be the most problematic expression of population ageing [6].

Whilst there is strong agreement that screening for frailty should be routinely undertaken [8], there is currently no consensus on the optimum operational definition of frailty, or the most appropriate assessment approach [9]. Significant progress has been made however, and two distinct approaches have been elaborated: the phenotype model [4], and the cumulative deficit model [10]. In the UK, the Electronic Frailty Index (eFI) is used as a measure of frailty in primary care electronic health care records, providing a simple yet effective mechanism for the identification of frailty within a practice population [11].

Harms of medicines with anticholinergic properties in older people

Anticholinergic medicines (with antimuscarinic properties) are routinely prescribed to treat a variety of clinical indications, despite being deemed high-risk and potentially inappropriate in the management of older people [12]. Through inhibition of the neurotransmitter acetylcholine by competitive binding to central and peripheral muscarinic receptors, anticholinergic activity can lead to a variety of commonly experienced side effects, which can be debilitating in these populations [13]. Problematic side effects include dry mouth, sedation, constipation and blurred vision, however there are also concerns over the longer-term adverse effects of these medicines [14]. Anticholinergic burden; defined as the cumulative effect of taking one or more medicines with anticholinergic properties [15], has emerged as a concept increasingly associated with physical dysfunction, cognitive decline, hospitalisation and mortality amongst older populations [16, 17], including those living with frailty [18]. As the evidence raises plausible concerns over the safety of these medicines in older people, it is imperative to understand which have anticholinergic properties, and how they can accumulate during the routine management of acute, and long-term conditions.

There is no consensus approach to the quantification of anticholinergic burden ,with various validated scales and indexes available to clinicians [17]. The scoring of medicines tends not to be exclusively derived by patient identified side effects, and instead expert opinion, pharmacological data, in vitro analyses of serum anticholinergic activity, or indeed a combination of approaches are adopted. The 2012 update of the Anticholinergic Cognitive Burden (ACB) scale has developed momentum for clinical use within UK healthcare settings [19], and is one of the most-frequently used expert opinion based scales for investigating adverse outcomes in observational research [16]. A score of 1 (possible anticholinergic activity), 2, or 3 (definite anticholinergic activity) is assigned to reflect increasing expected anticholinergic potency, and are summed to produce an ACB score; a numeric value quantifying anticholinergic burden. This simplicity makes it an attractive scale to characterise medicines within routine electronic health records [20].

We adapted the US-derived ACB scale in line with UK prescribing during the development of the AC-FRAIL tool, using an extensive list of UK specific anticholinergics developed by Richardson *et al*.[21].

NHS policy context

Within the UK's National Health Service (NHS), older people living with frailty are recognised as a priority group to ensure safe and effective prescribing [22]. The General Medical Services contract for England requires general practices to identify and manage patients over the age of 65 with moderate-to-severe frailty and conduct a medication review [22]. The first national service specification to be delivered by the Primary Care Networks (PCNs) in the 2020/21 period is 'Structured Medication Reviews (SMRs) and Optimisation Services'. To address this workload, the guidance encourages a targeted approach with the use of tools and technology, focusing on reducing overmedication [23].

The need for a case-finding tool

The NHS Business authority can provide practices with 'polypharmacy comparators' data using the ePACT2 platform; a high-level view of a practice prescribing to support proactive approaches to medicines management. This can highlight the percentage of patients exposed to higher ACB scores, or excessive polypharmacy for example, and although it is possible to make a request for the NHS numbers of these patients, it is not an activity that can be run easily within a practice as a tool to support medicines management. Neither is it able to stratify patients by frailty status. In EMIS Web, it is possible to identify ACB scores for individual medicines, but not as a systematic search of patients' total ACB scores across the practice population, and does not consider frailty. The AC-FRAIL tool is unique in how it proactively identifies anticholinergic burden amongst older people living with frailty within a practice population, by extracting data from a practice's clinical information system, and supporting users with decisions to prioritise medication reviews.

Introduction to the case-finding tool

The AC-FRAIL tool processes a standardised report from TPP SystmOne to produce graphical and tabular summaries of the relationship between the eFI and ACB scores. It is implemented in Microsoft Excel for ease of uptake within NHS practices (Microsoft v16.0 on Windows (32-bit) NT 10.00). The interactive user interface helps the user explore subgroups of their patient population according to two levels of ACB score, and three levels of frailty status.

Using the AC-Frail case-finding tool

As illustrated in figure 1, the user begins by running and exporting a prepared TPP SystmOne report. After clicking the 'Load Data' button in AC-FRAIL, the user selects the exported TPP SystmOne report from the explorer window, which is automatically loaded and processed. The relationship between ACB scores and the eFI is presented on a graphical display, where each point represents a patient (figure 2). The purpose of the graphical summary is to provide an overview of the practice's population, visualising the distribution of patients with mild, moderate and severe eFI scores and low or high ACB scores. The interactive buttons facilitate a detailed look at subgroups of patients in a tabular form, including information about the count and name of anticholinergic medications categorised according to the ACB scale. It is for the user to decide on which subgroup of patients to review first, however from the perspectives of theoretical risk, and in line with NHS guidance, it is recommended that the "High ACB – Severe eFI" group should be prioritised.

Search inclusion criteria

The extensive search was designed within TPP SystmOne's clinical reporting module. The search is limited to over 65-year olds, who are identifiable by TPP SystmOne's eFI report, and have been issued anticholinergic medicines within the previous three months. The structure of the clinical reports searching for the anticholinergic medicines can be visualised in figure 3. Patients are identified by the eFI report if they inherit at least one Read code characterising a frailty deficit. Anticholinergic medications can be of any class, licensed or unlicensed, and issues are not limited to those with repeat templates, allowing acute issues to be identified.

Incorporating anticholinergic burden and frailty

As of writing, automatic calculation of anticholinergic burden is not available within TPP SystmOne. Instead, the AC-FRAIL workflow uses multiple clinical reports separated by medicines that are collated for processing in the AC-FRAIL tool. Automated calculation of the eFI score is available in TPP SystmOne and is included in all clinical reports.

Thresholds for identifying high anticholinergic burden and frailty

Although there is limited evidence to suggest a threshold at which ACB scores become clinically significant, a score of 3 or more is deemed significant in terms of associations with adverse outcomes [21, 24]. AC-FRAIL uses an ACB threshold of 3 to indicate higher anticholinergic burden, and uses the eFI thresholds for which its validity was originally assessed: mild (>0.12 – 0.24), moderate (>0.24 – 0.36), and severe frailty (>0.36) [11].

Discussion

Advantages of the AC-FRAIL tool

The AC-FRAIL case-finding tool could help general practices identify individual patients with higher levels of anticholinergic burden, particularly those who are likely to be living with moderate to severe frailty. The tool has been designed for proactive searching of a practice's population. This is in accordance with NHS policy and the current primary-care strategy for frailty, and for the proactive delivery of SMRs in this target group [23].

Comparison with other tools

Other tools are available to support the quantification of anticholinergic burden, such as the web-based ACB calculator (http://www.acbcalc.com/), but this requires the manual input of medicines. EMIS Web provides functionality where individual medicines can be assigned an ACB score in a consultation, however cannot provide a total ACB score for all accumulated medicines, and cannot serve as a proactive audit function, stratifying by frailty. There is currently no functionality within TPP SystmOne for identifying anticholinergic burden.

We believe the AC-FRAIL tool is unique in its ability to identify potentially 'at risk' patients, by embracing a proactive approach through the screening of practice populations, quantifying ACB scores for all older people, and stratifying patients into subgroups based on frailty severity. This could be particularly attractive to PCNs when systematically targeting patients for SMRs, but also for quality improvement projects. The tool not only has the advantage of case-finding those at greater theoretical risk, but also identifying anticholinergic medicines, serving as an education resource to raise awareness of the vast array of anticholinergic medicines routinely prescribed.

The AC-FRAIL tool is also unique in how it can support practices in prioritisation of medication reviews. We would recommend prioritising the group with highest ACB Scores (≥3) and severe frailty (eFI > 0.36) for review, with the rationale that they could be imminently at risk of outcomes such as a fall, or delirium. However, a practice may prefer to review mild - moderately frail patients, with the focus on reducing the risk of worsening frailty, as there is evidence to suggest such medicines may influence frailty transitions [25].

Limitations of the tool

Although this tool can support systematic case-finding, it cannot substitute the clinical decision made by clinicians. It is limited to identifying possible 'at risk' patients, and

medicines to consider for dose reduction, optimisation, or substitution. As clinical judgement must be exercised, the tool should be seen as a resource to support the identification of 'at risk' patients, and support decision making around whether to review medications. The extensive anticholinergic medication list within the search is preliminary, despite comprehensively encompassing medicines within the ACB scale and further medicines, as per Richardson *et al.'s* updated list [21]. Searches for generic medicines do not incorporate all possible brands and branded generics within the data output, so it is necessary to add these to the searches, and update periodically, as well as any other anticholinergic formulations that come to market in the UK A formal review process will be developed to ensure searches remain up to date, informed by future updates to the ACB scale. Finally, the eFI score must not be interpreted as a diagnostic tool, and should be considered a screening tool only. Although the eFI demonstrates good sensitivity and specificity when identifying frailty at population level, it must be accompanied with clinical judgement by a trained professional when used at individual level to confirm the presence and severity. The eFI relies on accurate and up-to-date clinical coding, so inaccuracies can have implications on the validity of the eFI score.

Next steps for development

We initially intended to build the tool entirely within SystmOne, but the required features were not part of the clinical reporting functionality. In its current form as an Excel macro, the tool and the data it reads must be located on a local drive rather than a network drive, and each subgroup only handles up to 4,000 patients. Planned updates to the tool will address these issues and include a redesign of aesthetics and functionality. Improvements will be guided by user testing as part of ongoing work by the Safe Use of Medicines group at the NIHR Yorkshire and Humber Patient Safety Translational Research Centre, who will seek industry partners to develop a robust, national, vendor-neutral roll out. During 2019-2020, David Mehdizadeh is also undertaking a series of mixed-methods studies which will continue to inform the future development of the AC-FRAIL tool.

Declaration of interest

None to declare

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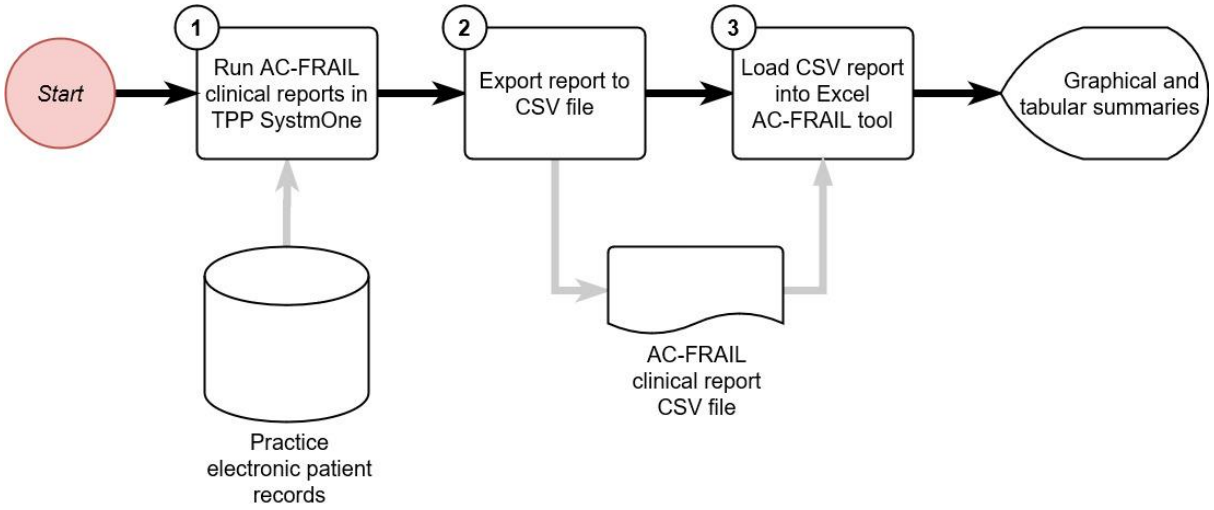

Figure 2: Graphical display of the relationship between ACB scores and the eFI, where each point represents a patient. The vertical grey bar marks the boundary for the ACB-score threshold and the horizontal black lines mark the boundaries of eFI thresholds: mild (>0.12 – 0.24), moderate (>0.24 – 0.36), and severe frailty (>0.36). Tabular summaries of subgroups can be accessed via the grey buttons that surround the plot.

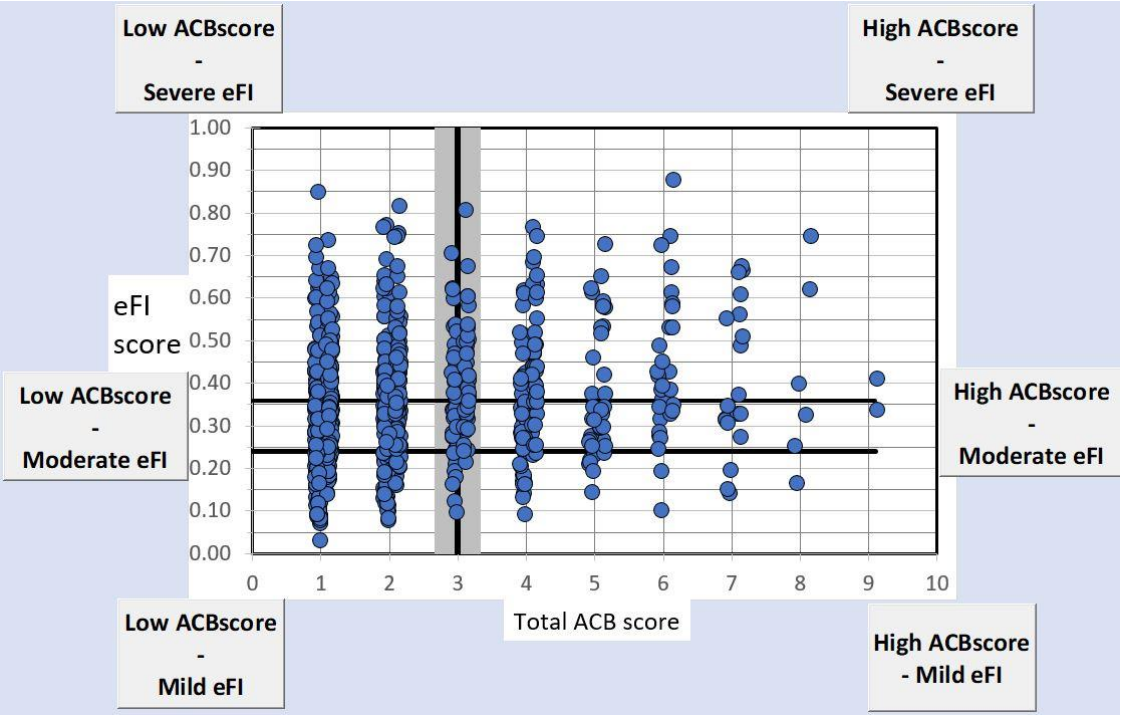

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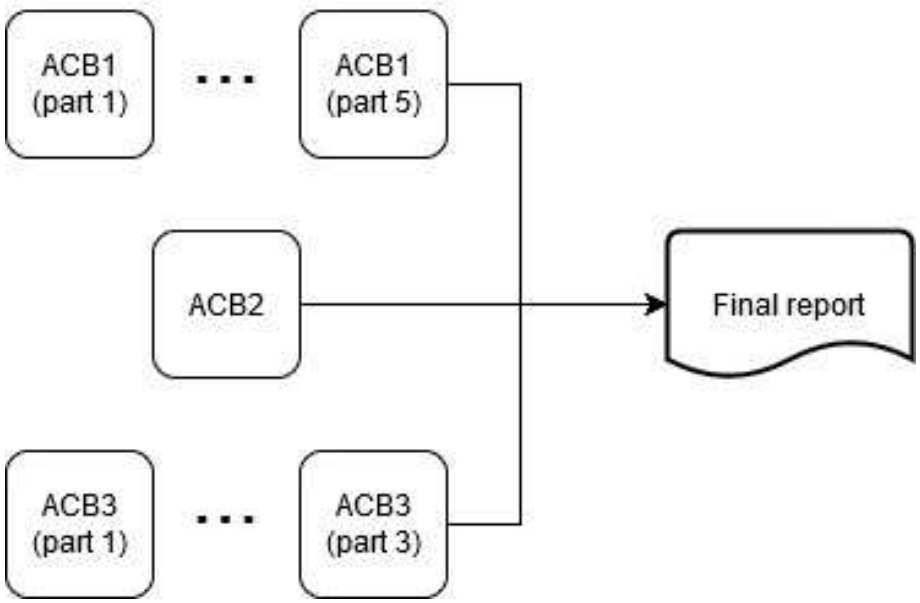
Figure 3: Diagram visualising how individual clinical reports were developed for the medicines, depending on their ACB score. There is a limit to the number of medicines that can be included within a single report, therefore multiple reports were created. They were then joined, so that patients taking any medicine, from any report, could be identified. Medicines had to be separated in to their respective ACB group, so that the final exported data file (CSV) could separate them into columns. This therefore supported the sum calculation for the total ACB score for a patient, performed by the AC-FRAIL tool.



References

1. Hilmer SN, Gnjidic D. Prescribing for frail older people. *Aust Prescr*. 2017;40(5):174-8.

2. Academy I. How to Guide: Joining the SystmOne Frailty Organisation Group & Downloading the STOPP Protocol 2015. https://improvementacademy.org/documents/Projects/healthy_ageing/STOPP%20SystmOne%20How%20to%20Guide.pdf. Accessed 10/02/2020.

3. Williams R, Keers R, Gude WT, Jeffries M, Davies C, Brown B et al. SMASH! The Salford medication safety dashboard. *BMJ Health & Care Informatics.* 2018;25(3):183.

4. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J et al. Frailty in older adults: evidence for a phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2001;56(3):M146-M57.

5. Song X, Mitnitski A, Rockwood K. Prevalence and 10-Year Outcomes of Frailty in Older Adults in Relation to Deficit Accumulation. *Journal of the American Geriatrics Society.* 2010;58(4):681-7.

6. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *The Lancet*. 2013;381(9868):752-62.

7. Speechley M, Tinetti M. Falls and injuries in frail and vigorous community elderly persons. *Journal of the American Geriatrics Society*. 1991;39(1):46-52.

8. Turner G, Clegg A. Best practice guidelines for the management of frailty: a British Geriatrics Society, Age UK and Royal College of General Practitioners report. Age and Ageing. 2014;43(6):744-7. doi:10.1093/ageing/afu138.

9. Rockwood K, Howlett SE. Fifteen years of progress in understanding frailty and health in aging. *BMC Medicine*. 2018;16(1):220. doi:10.1186/s12916-018-1223-3.

10. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *The Scientific World Journal*. 2001;1.

11. Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age and Ageing*. 2016;45(3):353-60.

12. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019;67(4):674-94.

13. Fox C, Smith T, Maidment I, Chan W-Y, Bua N, Myint PK et al. Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. *Age and ageing*. 2014;43(5):604-15.

14. Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. *European journal of clinical pharmacology*. 2013;69(7):1485-96.

15. Tune LE. Anticholinergic effects of medication in elderly patients. *The Journal of clinical psychiatry*. 2001;62 Suppl 21:11-4.

16. Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. *BMC Geriatrics*. 2015;15(1):31.

17. Welsh TJ, van der Wardt V, Ojo G, Gordon AL, Gladman JRF. Anticholinergic Drug Burden Tools/Scales and Adverse Outcomes in Different Clinical Settings: A Systematic Review of Reviews. *Drugs & aging*. 2018;35(6):523-38.

18. Landi F, Dell'Aquila G, Collamati A, Martone AM, Zuliani G, Gasperini B et al. Anticholinergic drug use and negative outcomes among the frail elderly population living in a nursing home. *Journal of the American Medical Directors Association*. 2014;15(11):825-9.

19. Campbell N, Maidment I, Fox C, Khan B, Boustani M. The 2012 Update to the Anticholinergic Cognitive Burden Scale.: C46. *Journal of the American Geriatrics Society*. 2013;61.

20. Lozano-Ortega G, Johnston KM, Cheung A, Wagg A, Campbell NL, Dmochowski RR et al. A review of published anticholinergic scales and measures and their applicability in database analyses. *Archives of Gerontology and Geriatrics*. 2020;87:103885.

21. Richardson K, Fox C, Maidment I, Steel N, Loke YK, Arthur A et al. Anticholinergic drugs and risk of dementia: case-control study. *BMJ*. 2018;361:k1315.

22. NHS England. Toolkit for general practice in supporting older people living with frailty. :NHS England, London.[Google Scholar]. 2017. https://www.england.nhs.uk/wp-content/uploads/2017/03/toolkit-general-practice-frailty-1.pdf. Accessed 10/07/2020 2020.

23. NHS England, BMA. Investment and evolution: a five-year framework for GP contract reform to implement the NHS long term plan. 2019. London: NHS England.

24. De Vreese LP, Mantesso U, De Bastiani E, Marangoni A, Weger E, Gomiero T. Anticholinergic burden in adult and elderly people with intellectual disabilities: Results from an Italian multicenter cross-sectional study. *PLoS One*. 2018;13(10):e0205897-e.

25. Jamsen KM, Bell JS, Hilmer SN, Kirkpatrick CM, Ilomäki J, Le Couteur D et al. Effects of Changes in Number of Medications and Drug Burden Index Exposure on Transitions Between Frailty States and Death: The Concord Health and Ageing in Men Project Cohort Study. *J Am Geriatr Soc*. 2016;64(1):89-95.