

PROFESSOR KELVIN JORDAN (Orcid ID : 0000-0003-4748-5335)

Article type : Original Article

Title: Indicators of dementia disease progression in primary care: an electronic health record cohort study

Authors

Trishna Rathod-Mistry¹, Michelle Marshall¹, Paul Campbell^{1,2}, James Bailey¹, Carolyn A Chew-Graham^{1,2}, Peter Croft¹, Martin Frisher³, Richard Hayward¹, Rashi Negi², Louise Robinson⁴, Swaran Singh⁵, Athula Sumathipala^{1,2}, Nwe Thein², Kate Walters⁶, Scott Weich⁷, Kelvin P Jordan^{1,8*}

Affiliations

¹School of Medicine, Keele University, UK

²Midlands Partnership NHS Foundation Trust, Stafford, UK

³School of Pharmacy and Bioengineering, Keele University, UK

⁴Institute of Health and Society and Newcastle University Institute for Ageing, UK

⁵Division of Mental Health and Wellbeing, Warwick Medical School, University of Warwick, UK

⁶Research Department of Primary Care & Population Health, University College London, UK

⁷Mental Health Research Unit, School of Health and Related Research (ScHARR), University of Sheffield, UK

⁸Centre for Prognosis Research, Keele University, UK

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ENE.14710](https://doi.org/10.1111/ENE.14710)

This article is protected by copyright. All rights reserved

***Corresponding author:** Kelvin Jordan, School of Medicine, Keele University, Staffordshire ST5 5BG, UK. Tel. +44 1782 733924. Email: k.p.jordan@keele.ac.uk

Total word count including title page, abstract and references: 5723

Word count for Introduction, Methods, Results, Discussion: 3499

Disclosure: None

Short running title: Indicators of dementia disease progression

Keywords: Dementia, Prognosis, Electronic Health Records, Primary Care, Outcomes

Abstract

Background The objectives were to assess the feasibility and validity of using markers of dementia-related health as indicators of dementia progression in primary care, by assessing the frequency they are recorded and by testing the hypothesis they are associated with recognised outcomes of dementia. The markers, in 13 domains, were derived previously through literature review, expert consensus, and analysis of regional primary care records.

Methods The study population were patients with a recorded dementia diagnosis in the Clinical Practice Research Datalink, a UK primary care database linked to secondary care records.

Incidence of recorded domains in the 36 months after diagnosis was determined. Associations of recording of domains with future hospital admission, palliative care, and mortality were derived.

Results There were 30,463 people with diagnosed dementia. Incidence of domains ranged from 469/1000 person-years (Increased Multimorbidity) to 11/1000 (Home Pressures). An increasing number of domains in which a new marker was recorded in the first year after diagnosis was associated with hospital admission (hazard ratio for ≥ 4 domains versus no domains 1.24; 95% CI 1.15, 1.33), palliative care (1.87; 1.62, 2.15), and mortality (1.57; 1.47, 1.67). Individual domains were associated with outcomes with varying strengths of association.

Conclusions

Feasibility and validity of potential indicators of progression of dementia derived from primary care records is supported by their frequency of recording and associations with recognised outcomes. Further research should assess whether these markers can help identify patients with poorer prognosis in order to improve outcomes through stratified care and targeted support.

Introduction

Over 850,000 people in the UK are estimated to live with dementia, projected to rise to 1.6million by 2040.¹ Dementia has a substantial impact on the lives of individuals. The UK government has prioritised early recognition and treatment, in order to prolong independence, delay and reduce admissions to nursing home and hospital, and prolong survival.²⁻⁴ Primary care has a pivotal role in achieving these aims,⁵⁻⁷ particularly in the UK where most people are registered with a general practitioner (GP) and receive care for long-term conditions.

There have been primary care studies on “case-finding” and identifying risk factors for dementia onset,^{8,9} but little research on the course and prognosis of patients with dementia in primary care. One potential source of information on the course of dementia are primary care electronic health records (EHR) that contain coded reasons (morbidities, symptoms) for consultation and management (for example, prescriptions, referrals, tests, investigations). While EHR can provide data on “hard” long-term outcomes such as hospital admissions and mortality, it is not known whether indicators of disease progression can be identified from primary care EHR.

A set of indicators in primary care could support case management decisions, contribute to understanding of prognosis, improve communication with patients and caregivers, and inform planning and monitoring of care at a population level. They could improve the efficiency of intervention studies which currently rely on intensive and costly follow-up assessments and long-term outcomes such as mortality. In the first part of the MEasurement of Dementia Disease progression in Primary care (MEDDIP) study, we established a set of markers of dementia-related health that may be recorded in UK primary care EHR,¹⁰ drawing on a rapid literature review, expert consensus, and scrutiny of a regional primary care EHR database. The set has 63 markers in 13 domains (Table 1).

The objectives of this part of the MEDDIP study were to assess the feasibility and validity of these markers and domains as indicators of progression for people with dementia. Feasibility was assessed by estimating the prevalence and incidence of recorded markers and domains within primary care EHR at time of, and early after, diagnosis of dementia. Validity was assessed by estimating the association of recording of these domains with established longer-term outcomes (hospital admission, palliative care, early mortality) under the hypothesis (construct validity) that patients with new recorded markers/domains early on in their dementia course will have a higher risk of poor outcomes.

Methods

Setting

This was a cohort study set within the Clinical Practice Research Datalink (CPRD) GOLD, a database of longitudinal pseudonymised primary care data from 17 million patients across a network of UK general practices. The study was approved by the CPRD Independent Scientific Advisory Committee (ref 19_002).

Study population

Patients with a recorded diagnosis of Alzheimer's disease, vascular dementia, Lewy Body dementia, Parkinson's dementia, fronto-temporal dementia, mixed, and unspecified dementia between 1998-2017 were included. Diagnosis of dementia was based on a Read code list developed previously through consensus of GP and EHR researchers,¹¹ and code lists used in other studies.¹²⁻¹⁴ Read codes are the main method of recording morbidity and processes of care within UK primary care. Coding of dementia in UK primary care EHR has been validated previously.¹⁵ Patients with a Read code suggesting a history of any type of dementia (for example, "H/O: (History of) dementia", "Dementia annual review") prior to the date of first dementia diagnosis (index date) or a recorded prescription for an anti-dementia drug (Donepezil, Galantamine, Memantine, Rivastigmine) prior to the index date were excluded. Read code lists are available from www.keele.ac.uk/mrr.

Patients had to have three years of up to standard data in CPRD prior to the index date and one year post index date as a minimum follow-up time to capture progression of dementia (Figure 1a). All patients were required to have linked Hospital Episode Statistics (HES) admissions, neighbourhood deprivation (Index of Multiple Deprivation 2015¹⁶), and mortality (via the Office for National Statistics [ONS]) data. This encompasses around 50% of patients in CPRD GOLD (all in England).

Markers and domains

Code lists for markers utilised previous UK-based EHR research studies,¹⁷⁻²⁴ existing databases of Read code lists,^{25,26} and searches of the UK Clinical Terminology Read Code Browser. The markers and associated domains are shown in Table 1. The first recording of each marker in the period from two years before the index date to three years after was identified. The exception was for the Increased Multimorbidity domain which was measured for each 12-month period within those five years and is a general measure of multimorbidity (increase in number of different drugs prescribed, based on British National Formulary sections, compared to the previous 12-month period). The Dementia-related Drug domain was based on a new prescribed drug specific to dementia (Donepezil, Galantamine, Memantine, Rivastigmine) or a drug that may be used in dementia as well as other conditions (Levodopa, Clonazepam, Rotigotine, Selegiline, Rasagiline, Apomorphine).

Outcomes

The outcomes were first all-cause hospital admission, palliative care, and all-cause mortality measured until the end of follow-up defined as earliest of date of death, end of study (December 31st 2018), and date of end of up-to-standard records in CPRD. Hospital admission from any cause was based on recorded date of admission in the linked HES data after diagnosis. Palliative care was defined based on Read coded indication of palliative care or coded indication of being within 12 months of end of life.²⁷ Patients with such a Read code prior to the index date were excluded from analysis of this outcome. All-cause mortality was defined as the earliest record of death from CPRD or ONS mortality data.

Baseline covariates

Covariates were age at index date, sex, year of diagnosis, geographical region, deprivation, and lifestyle factors. Deprivation was measured by the Index of Multiple Deprivation 2015, a composite measure of neighbourhood deprivation.¹⁶ Lifestyle factors (body mass index, smoking status, alcohol consumption) were based on the most recent measurement in the five years prior to the index date.

Analysis

Time periods for each analysis are shown in Figure 1. When analysing associations with outcomes, markers and domains were measured prior to occurrence of that outcome.

Feasibility: Prevalence and incidence of markers and domains

The prevalence of recorded markers at time of diagnosis, defined as the proportion of all people in the study population with a record of the marker in the 24 months prior to the index date, was determined. Incidence per 1000 person-years (py) at risk of recorded markers in the 36 months after the index date in those with no record of the marker in the 24 months prior to index date was determined (Figure 1b). Prevalences and incidences of domains were also calculated. Incidence was defined for 12 domains as a record of any marker in the domain after index date with no previous record of any marker from that domain. For the remaining domain, a first increase in the number of different drugs prescribed in a 12 month period compared to the previous 12 months indicated increased multimorbidity

Validity: Associations of domains with outcomes

Associations of domains with outcomes were assessed in two ways. First, we examined the associations of individual domains recorded up to three years after diagnosis (but before outcome). The incidence after index date of each of the outcomes (hospital admission, palliative care, mortality) per 1000py at risk were calculated. Cox proportional hazards models estimated the association of having any recorded marker in a domain with each outcome, adjusted for age and gender. The proportional hazards assumption was visually assessed using (log-log transformed) survival curves. Domain (exposure) was included as a time varying covariate. Follow-up started at index date and baseline exposure was defined as a record of any marker within the domain in the 24 months prior to the index date and exposure status could change from unexposed at baseline to exposed over the first three years of follow-up (Figure 1c). It was assumed that, once the patient was exposed (i.e. had a record of any marker from that domain), they were exposed for the remainder of follow-up (until censored or outcome occurred). As Increased Multimorbidity was defined over a 12 month period, date of changed exposure was the end of the 12 month period i.e. 1, 2 or 3 years after the index date.

Validity: Accumulation of markers and association with outcomes

Our second approach to examine associations of domains with outcomes assessed the relationship of accumulation of new markers early after diagnosis with outcomes. For this analysis, for most domains, a record of any previously unrecorded marker in a domain indicated progression even if another marker within that domain had previously been recorded. The Daily Functioning domain has a hierarchical subset of markers (Mobility-limited, Mobility-severe, Wheelchair, Bedbound), and a marker was counted only if a more restricted mobility marker had not previously been used. In the Safety domain any fall was counted regardless of previously recorded falls. For each patient we determined the cumulative number of domains with at least one marker that was first recorded in the 12 months after the index date (i.e. no record of that marker in the 24m prior to the index date, even if other markers in that domain had been recorded). Follow-up of outcomes started at 12 months post-index date (Figure 1d). Cox proportional hazards models determined the association of cumulative number of domains in that first 12 months with the outcomes adjusted for baseline covariates. Analysis was repeated for cumulative number of domains over the 36 months after index date in those with at least 36 months of follow-up, with follow-up of outcomes starting at 36 months. Robustness of estimates was assessed by repeating the analysis using flexible parametric models.

Sensitivity analyses assessed whether any improvement in completeness of recording of markers over time influenced results by restricting the analysis to patients diagnosed with dementia from 2010 onwards.

All analyses were performed in Stata v15.

Results

30,463 patients with dementia met our inclusion criteria. Baseline patient characteristics are given in table 2. Mean age was 81.6 (SD 7.86) years and 63% were female. Median follow-up was 2.73 (interquartile range 1.75, 4.24) years. The majority (96% of those with a type recorded) of dementia patients were diagnosed with Alzheimer's or vascular dementia.

Prevalence and incidence of markers and domains

In the 24 months prior to index (diagnosis) date, 68% of patients had at least one recorded marker from the Comorbidity domain and 62% from the Cognitive Function domain (Table 3). Home Pressures (4%) and Care (5%) were the least prevalent domains.

Increased Multimorbidity (based on increase in polypharmacy) was the most common domain newly recorded after index date. The highest incidence for the other domains was observed for Comorbidity (300/1000py), and Symptoms (230/1000py). Home Pressures had the lowest incidence (11/1000py). Prevalence and incidence of markers are reported in Supplementary table A1.

Associations of domains with outcomes

74% of patients were hospitalised at least once after index date (430/1000py; 95% CI: 424, 436), 8% of patients received palliative care (26/1000py; 95% CI: 25, 27) and 37% of patients died (115/1000py; 95% CI: 112, 116) during follow-up.

The majority of domains were associated with increased risk of all three outcomes (Table 4). The Safety, Comorbidity, and Symptoms domains had the strongest associations with hospital admission (hazard ratios (HRs) 1.36 to 1.40), whilst the Severe Neuropsychiatric, Diet/Nutrition, Increased Multimorbidity and Daily Functioning domains had strongest associations with palliative care (HRs 1.97-2.23) and mortality (HRs 1.92-2.84). The Home Pressures domain was only associated with palliative care. The Cognitive Function domain was negatively associated

with hospital admission (HR 0.94; 95% CI 0.91, 0.97) and mortality (HR 0.95; 95% CI 0.92, 0.99). A new or change in dementia-related drug was protective of all three outcomes.

Accumulation of markers and association with outcomes

In the 12 months after index date, 26,055 (86%) of patients had at least one recorded marker not previously recorded, and 5,594 (18%) had at least four domains with a new recorded marker.

Increasing number of domains with new recorded markers in the one year post-index date was linearly associated with increasing risk of hospital admission, palliative care, and mortality (Table 5). Adjusted HRs when comparing patients with new markers in four or more domains to patients with no new recorded markers were 1.24 (95% CI 1.15, 1.33) for hospital admission, 1.87 (95% CI 1.62, 2.15) for palliative care, and 1.57 (95% CI 1.47, 1.67) for mortality. Restricting analysis to the 15,123 patients diagnosed with dementia from 2010 onwards gave similar strengths of association (Supplementary table A2).

Sensitivity analysis exploring the associations between domains recorded in the three years after index date with outcomes after three years provided similar results. HRs for the comparison of patients with four or more domains with newly recorded markers compared to those with no domains were 1.28 (95% CI 1.05, 1.57) for hospital admission, 2.31 (95% CI 1.27, 4.19) for palliative care, and 1.64 (95% CI 1.33, 2.03) for mortality (Supplementary table A3). Repeating the main analyses using flexible parametric models yielded similar hazard ratios to the Cox proportional hazards models (Supplementary table A4).

Discussion

This study of over 30,000 patients with dementia in England aimed to determine the feasibility and validity of using markers of dementia-related health as indicators of dementia progression in primary care. The study showed that these markers, nested in domains, can be identified in primary care EHR, and their recording are associated with recognised endpoint outcomes (hospital admission, palliative care, mortality). There was a dose response effect after diagnosis, with an increase in risk of poor outcomes as the number of domains for which new markers were recorded soon after diagnosis increased. These results demonstrate the potential to identify indicators of progression for those with dementia using primary care EHR.

Whilst there was variation in their prevalence and incidence, all domains had evidence of regular recording in primary care. However, some individual markers were infrequently recorded and use of these markers as indicators of progression may be more feasible at the domain-level. Construct validity of the domains was shown through testing of an a priori hypothesis of their association with recognised outcomes. A record of a marker such as psychosis within the Severe Neuropsychiatric domain increased risk of all outcomes, concordant with a previously identified link of behavioural and psychological symptoms and/or anti-psychotic use with risk of hospitalisation, nursing home admission, and mortality.²⁸⁻³¹ The Increased Multimorbidity, Comorbidity, and Symptoms domains were commonly recorded and strongly associated with the outcomes; supporting reviews showing increases in comorbidity and health-related burden related to poor dementia outcomes.^{30,32,33} The Care domain showed associations across all outcomes; research shows that caregiver coping and stress is associated with poor outcomes in the person with dementia,^{30,34} but also will be reflective of increased provision of care as demonstrated by the strong association with palliative care.

Having a record of a marker (for example, cognitive decline or memory loss) from the Cognitive Function domain did not increase risk of the outcomes. One explanation for this might be the level of information available. A recent EHR study interrogated narrative text (i.e. clinical notes) to give a gradient of cognitive function severity and demonstrated that greater severity is associated with mortality.³⁵ A finer grade indicator inclusive of severity would be beneficial in the prediction of outcomes. It is also possible cognitive function is less commonly assessed or completed when the patient is nearing end of life,³⁶ or that non-cognitive measures are more strongly associated with the outcomes used here.

A prescription for a new dementia-related drug was associated with a reduced risk of the outcomes. Previous research has shown that use of cholinesterase inhibitors is associated with lower mortality in people living with Alzheimer's disease.^{37,38} This domain does not take into account reason for change or whether change was to a more or less potent drug (related to stage of dementia) and therefore may be a less valid indicator of progression.

The domains of Daily Functioning, Diet/Nutrition, and Safety showed consistent associations with our outcomes which concurs with research that has shown associations between functional ability and mortality,³⁹ and nutrition and outcomes for those with dementia,⁴⁰ and is reflective of broader function, safety issues (e.g. falls) and frailty in elderly populations.^{41,42}

Strengths and Limitations

This study tested a rigorously developed set of domains previously demonstrated to be associated with dementia. These domains had been produced via a review of EHR dementia research and expert consensus to ensure clinical relevance, mapped to an internationally agreed set of outcomes,⁴³ and initial testing within a regional EHR database.¹⁰ The CPRD database is broadly reflective of the UK population⁴⁴ with established validity for coding and accuracy of dementia diagnosis.⁴⁵ Whilst measures of frailty designed for use within EHR for the elderly population⁴¹ may overlap with some of the domains, we have derived domains specifically relevant to dementia. Future studies could compare our indicators of early progression with general measures of frailty.

Lewy Body and fronto-temporal dementia are associated with greater behavioural disturbance and have a faster progression rate to mortality.^{46,47} Given these types of dementia are less common, larger studies should compare indicators of progression by dementia-type. Whilst a person may consult with a number of problems, the clinician might decide to only code one problem. A coded record for a marker would suggest this was a key reason for a consultation and of importance to the clinician and patient/caregiver. Some markers may have been recorded prior to the window of time we examined, and whilst most chronic problems should be entered on a regular basis our markers reflect recent issues. It is possible that some markers in a domain may be acute in nature and have less impact on long-term outcomes. Some markers could be sequentially related (e.g. a fall before a fracture), or have a gradient of severity (e.g. neuropsychiatric). This study aimed to determine the validity of markers and domains as indicators of progression, and not as independent predictors of poor outcome. As such, some of the associations identified with long term outcomes may have arisen through chance given the multiple testing, and there may be other factors predictive of poor outcome including socio-economic status, ethnicity, social support, social care provision,^{24,30,32,33,48,49} and measures obtainable by invasive testing such as pathogen presence (e.g. CSF t-tau) and cortical atrophy (volumetric MRI). Future prognostic research should assess which domains improve prediction of long-term outcomes when added to other factors. Such research would need to address the potential for collinearity between domains. We could not use care home admission as an outcome as this is not comprehensively recorded in primary care EHR. Future studies could compare recording of these markers and domains with

changes on instruments designed to measure cognitive function such as the Mini-Mental State Examination, commonly used in secondary care dementia services.

Clinical Relevance

This study is a key step in the development of an approach for managing people with dementia, where individuals who are at increased risk of a poor health outcome can be identified in a primary care setting. This has potential advantages. First, good information on prognosis can contribute to shared decisions on care between patients, carers, and clinicians. Second, “dementia” often overshadows other comorbidities within the consultation,^{50,51} and systematic information about such additional concerns contributes to more holistic approaches to care^{52,53} and better healthcare coordination. Third, early identification and targeted care using a stratified-risk approach within the primary care population with dementia may offer the possibility of intervening to slow progression. This may either be by concentrating resources on patients with higher risk of poor outcomes or, if these markers and domains can be shown to be independent predictors of poor outcome, by targeting those that are modifiable such as prescribing.

The increase in risk as number of domains with new markers increases suggests that, whilst some domains had stronger associations with outcomes than others, it is the cumulative burden of indicators rather than particular combinations which increases risk of poor outcomes. This may advocate a simple approach to monitoring early dementia progression based on count of new indicators as measured by our domains.

These indicators may be useful in prognostic models to improve identification of patients with a poorer long-term outcome. It may be possible in the future to use these EHR-recorded markers and domains as short-term outcomes, reducing the time and costs of research studies, given that dementia observational and intervention studies often have to use long-term outcomes such as mortality and care home admission.

Conclusions

The validity of potential indicators of progression of dementia derived from primary care EHR is supported by their association with recognised outcomes. In particular, early accumulation of these indicators after diagnosis is associated with hospital admission, palliative care and mortality.

Combined with their prevalence and incidence in primary care EHR that illustrate their potential

feasibility for use in practice, our study has established a case for future investigation of whether this set of markers can be applied to identify patients with a poorer long-term prognosis in order to improve their outcomes through stratified care and targeted support.

Funding

This study was funded by The Dunhill Medical Trust [RPGF 1711/11] as part of The MEasurement of Dementia DIsease progression in Primary care (MEDDIP) study. KJ and CCG are also supported by matched funding awarded to the NIHR Applied Research Collaboration (West Midlands). The views and opinions expressed are those of the authors and not necessarily the views of The Dunhill Medical Trust, NHS, the NIHR or the Department of Health and Social Care.

Acknowledgements

The study team would like to acknowledge the Patient and Public Involvement and Engagement Dementia Group within the School of Medicine for their input into the development and management of the overall MEasurement of Dementia DIsease Progression in Primary care (MEDDIP) project, of which this study is a part. The study team would also like to thank the project steering group for the MEDDIP study. This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. Use of HES and ONS data: copyright ©2019, re-used with the permission of The Health & Social Care Information Centre. All rights reserved.

Ethical approval

Study approved by the CPRD Independent Scientific Advisory Committee, ref 19_002.

Data Sharing

The data that support the findings of this study are available from the Clinical Practice Research Datalink (www.cprd.com). Restrictions apply to the availability of these data. Access is subject to protocol approval by an Independent Scientific Advisory Committee (ISAC).

Table / Figure legends

Table 1. List of markers nested within domains with examples

Table 2. Characteristics of patients with dementia, $n=30,463$

Table 3. Prevalence and incidence of recorded domains

Table 4. Associations of recording of domains with hospital admission, palliative care, and mortality

Table 5. Association of the cumulative number of domains with new recorded markers in the first year after diagnosis with hospital admission, palliative care, and mortality after the first year

Figure 1. Time windows for the study

References

1. Wittenberg R, Hu B, Barraza-Araiza L, Rehill A. Projections of older people with dementia and costs of dementia care in the United Kingdom, 2019–2040. 2019, Care Policy and Evaluation Centre, London School of Economics and Political Science, London.
2. Abdi Z, Burns A. Championing of dementia in England. *Alzheimer's Research & Therapy* 2012;4(5):1-3.
3. Department of Health. Living well with dementia: A national dementia strategy. *Department of Health*; 2009.
4. Dodd E, Cheston R, Ivanecka A. The assessment of dementia in primary care. *Journal of Psychiatric and Mental Health Nursing* 2015;22(9).
5. Greaves I, Greaves N, Walker E, Greening L, Benbow SM, Jolley D. Gnosall primary care memory clinic: eldercare facilitator role description and development. *Dementia* 2015;14(4):389-408.
6. Thyrian JR, Eichler T, Pooch A, et al. Systematic, early identification of dementia and dementia care management are highly appreciated by general physicians in primary care—results within a cluster-randomized-controlled trial (DelpHi). *Journal of Multidisciplinary Healthcare* 2016;9:183.
7. Dening KH. Recognition and assessment of dementia in primary care. *British Journal of Community Nursing* 2019;24(8):383-7.
8. Walters K, Hardoon S, Petersen I, et al. Predicting dementia risk in primary care: development and validation of the Dementia Risk Score using routinely collected data. *BMC Medicine* 2016;14(1):6.
9. Ford E, Greenslade N, Paudyal P, et al. Predicting dementia from primary care records: a systematic review and meta-analysis. *PLoS One* 2018;13(3):e0194735.

10. Campbell P, Rathod-Mistry T, Marshall M, et al. Markers of dementia-related health in primary care electronic health records. *Aging and Mental Health* 2020, early online release (DOI:1080/13607863.2020.1783511).
11. Burton C, Campbell P, Jordan K, Strauss V, Mallen C. The association of anxiety and depression with future dementia diagnosis: a case-control study in primary care. *Family Practice* 2013;30(1):25-30.
12. Brown A, Kirichek O, Balkwill A, et al. Comparison of dementia recorded in routinely collected hospital admission data in England with dementia recorded in primary care. *Emerging Themes in Epidemiology* 2016;13(1):11.
13. Browne J, Edwards DA, Rhodes KM, Brimicombe DJ, Payne RA. Association of comorbidity and health service usage among patients with dementia in the UK: a population-based study. *BMJ Open* 2017;7(3):e012546.
14. Pham TM, Petersen I, Walters K, et al. Trends in dementia diagnosis rates in UK ethnic groups: analysis of UK primary care data. *Clinical Epidemiology* 2018;10:949.
15. Pujades-Rodriguez M, Assi V, Gonzalez-Izquierdo A, et al. The diagnosis, burden and prognosis of dementia: A record-linkage cohort study in England. *PloS One* 2018;13(6):e0199026.
16. Smith T, Noble M, Noble S, Wright G, McLennan D, Plunkett E. The English indices of deprivation 2015. London: *Department for Communities and Local Government* 2015 Sep.
17. Baker NL, Cook MN, Arrighi HM, Bullock R. Hip fracture risk and subsequent mortality among Alzheimer's disease patients in the United Kingdom, 1988–2007. *Age and Ageing* 2011;40(1):49-54.
18. Davies NM, Kehoe PG, Ben-Shlomo Y, Martin RM. Associations of anti-hypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias. *Journal of Alzheimer's Disease* 2011;26(4):699-708.
19. Grant RL, Drennan VM, Rait G, Petersen I, Iliffe S. First diagnosis and management of incontinence in older people with and without dementia in primary care: a cohort study using The Health Improvement Network primary care database. *PLoS Med.* 2013;10(8):e1001505.
20. Imfeld P, Bodmer M, Schuerch M, Jick SS, Meier CR. Risk of incident stroke in patients with Alzheimer disease or vascular dementia. *Neurology* 2013;81(10):910-9.
21. Cook M, Baker N, Lanes S, Bullock R, Wentworth C, Arrighi HM. Incidence of stroke and seizure in Alzheimer's disease dementia. *Age and Ageing* 2015;44(4):695-9.

22. Guthrie B, Clark SA, McCowan C. The burden of psychotropic drug prescribing in people with dementia: a population database study. *Age and Ageing* 2010;39(5):637-42.
23. Dennis M, Shine L, John A, et al. Risk of adverse outcomes for older people with dementia prescribed antipsychotic medication: a population based e-cohort study. *Neurology and Therapy* 2017;6(1):57-77.
24. Lewis G, Werbeloff N, Hayes JF, Howard R, Osborn DP. Diagnosed depression and sociodemographic factors as predictors of mortality in patients with dementia. *The British Journal of Psychiatry* 2018;213(2):471-6.
25. Springate DA, Kontopantelis E, Ashcroft DM, et al. ClinicalCodes: an online clinical codes repository to improve the validity and reproducibility of research using electronic medical records. *PloS One* 2014;9(6):e99825.
26. Keele Medical Record Research website. www.keele.ac.uk/mrr. Accessed 6th July 2020.
27. General Medical Council. Treatment and care towards the end of life: good practice in decision making Available from: www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/treatment-and-care-towards-the-end-of-life. Accessed 24th June 2020.
28. Gill SS, Bronskill SE, Normand SL, et al. Antipsychotic drug use and mortality in older adults with dementia. *Annals of Internal Medicine* 2007;146(11):775-86.
29. Banerjee S. The use of antipsychotic medication for people with dementia. Time for action. A report for the Minister of State for Care Services. 2009. *Department of Health*: <http://webarchive.nationalarchives.gov.uk>. (accessed June 2020).
30. Modrego PJ, Lobo A. Determinants of progression and mortality in Alzheimer's Disease: a systematic review. *Neuropsychiatry (London)* 2018;8(5):1465-75.
31. Ralph SJ, Espinet AJ. Increased all-cause mortality by antipsychotic drugs: updated review and meta-analysis in dementia and general mental health care. *Journal of Alzheimer's Disease Reports* 2018;2(1):1-26.
32. McMichael AJ, Zafeiridi E, Passmore P, Cunningham EL, McGuinness B. Factors associated with mortality including nursing home transitions: a retrospective analysis of 25,418 people prescribed anti-dementia drugs in Northern Ireland. *Journal of Alzheimer's Disease* 2020;73(3):1233.
33. Bandosz P, Ahmadi-Abhari S, Guzman-Castillo M, et al. Potential impact of diabetes prevention on mortality and future burden of dementia and disability: a modelling study. *Diabetologia* 2020;63(1):104-15.

34. Lwi SJ, Ford BQ, Casey JJ, Miller BL, Levenson RW. Poor caregiver mental health predicts mortality of patients with neurodegenerative disease. *Proceedings of the National Academy of Sciences* 2017;114(28):7319-24.
35. McCoy Jr TH, Han L, Pellegrini AM, Tanzi RE, Berretta S, Perlis RH. Stratifying risk for dementia onset using large-scale electronic health record data: A retrospective cohort study. *Alzheimer's & Dementia* 2020;16(3):531-40.
36. Rockwood K, Jones D, Wang Y, Carver D, Mitnitski A. Failure to complete performance-based measures is associated with poor health status and an increased risk of death. *Age and Ageing* 2007;36(2):225-8.
37. Lopez OL, Becker JT, Wisniewski S, Saxton J, Kaufer DI, DeKosky ST. Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry* 2002;72(3):310-4.
38. Ku LJ, Li CY, Sun Y. Can persistence with cholinesterase inhibitor treatment lower mortality and health-care costs among patients with Alzheimer's disease? A population-based study in Taiwan. *American Journal of Alzheimer's Disease & Other Dementias* 2018;33(2):86-92.
39. Mahmoudi R, Novella JL, Manckoundia P, et al. Is functional mobility an independent mortality risk factor in subjects with dementia?. *Maturitas* 2017;103:65-70.
40. de Sousa OV, Mendes J, Amaral TF. Nutritional and functional indicators and their association with mortality among older adults with Alzheimer's Disease. *American Journal of Alzheimer's Disease & Other Dementias* 2020;35:1533317520907168.
41. 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(3):353-60.
42. Sharma S, Mueller C, Stewart R, et al. Predictors of falls and fractures leading to hospitalization in people with dementia: a representative cohort study. *Journal of the American Medical Directors Association* 2018;19(7):607-12.
43. International Consortium for Health Outcomes Measurement. The ICHOM Standard Set for Dementia 2016 (London, UK).
44. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research datalink (CPRD). *International Journal of Epidemiology* 2015;44(3):827-36.
45. McGuinness LA, Warren-Gash C, Moorhouse LR, Thomas SL. The validity of dementia diagnoses in routinely collected electronic health records in the United Kingdom: A systematic review. *Pharmacoepidemiology and Drug Safety* 2019;28(2):244-55.

46. Garcia-Ptacek S, Farahmand B, Kåreholt I, Religa D, Cuadrado ML, Eriksdotter M. Mortality risk after dementia diagnosis by dementia type and underlying factors: a cohort of 15,209 patients based on the Swedish Dementia Registry. *Journal of Alzheimer's Disease* 2014;41(2):467-77.
47. Mueller C, Soysal P, Rongve A, et al. Survival time and differences between dementia with Lewy bodies and Alzheimer's disease following diagnosis: A meta-analysis of longitudinal studies. *Ageing Research Reviews* 2019;50:72-80.
48. Yaffe K, Fox P, Newcomer R, et al. Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA* 2002;287(16):2090-7.
49. Gaugler JE, Duval S, Anderson KA, Kane RL. Predicting nursing home admission in the US: a meta-analysis. *BMC Geriatrics* 2007;7(1):13.
50. Jones S, Howard L, Thornicroft G. 'Diagnostic overshadowing': worse physical health care for people with mental illness. *Acta Psychiatrica Scandinavica* 2008;118(3):169-71.
51. Subramaniam H. Co-morbidities in dementia: time to focus more on assessing and managing co-morbidities. *Age and Ageing* 2019;48(3):314.
52. Apesoa-Varano EC, Barker JC, Hinton L. Curing and caring: the work of primary care physicians with dementia patients. *Qualitative Health Research* 2011;21(11):1469-83.
53. Macfarlane S, Cunningham C. The need for holistic management of behavioral disturbances in dementia. *International Psychogeriatrics* 2017;29(7):1055-8.

Table 1. List of markers nested within domains with examples

Domain	Marker	Examples
Care	Additional Help	Home help, day care
Care	Carer	Evidence has a carer in records
Care	Shared Decision Making	Shared decision making
Care	Advanced Directive	Advanced care planning
Home Pressures	Home Pressures	Marital problems, family bereavement/row
Severe Neuropsychiatric	Severe Mental Illness – (a) coded	Psychosis, schizophrenia
Severe Neuropsychiatric	Severe Mental Illness – (b) medication	Anti-psychotic drug
Severe Neuropsychiatric	Sectioned	Sectioned Form completed/fee paid
Severe Neuropsychiatric	Crisis	Mental crisis plan, referral to crisis team
Severe Neuropsychiatric	Suicidal	Suicidal, high/medium suicide risk
Neuropsychiatric	Depression, Anxiety, Stress – (a) coded	Depression, anxiety, stress
Neuropsychiatric	Depression, Anxiety, Stress – (b) medication	Anti-depressant drug
Neuropsychiatric	Aggressive Behaviour	Aggressive/abusive behaviour
Neuropsychiatric	Sleep Problems – (a) coded	Insomnia, nightmares
Neuropsychiatric	Sleep Problems – (b) medication	Hypnotic/anxiolytic drug
Neuropsychiatric	Behavioural Issues	Behavioural problem, disinhibited behaviour
Neuropsychiatric	Low Mood	Low mood, tearful, worried, lack of concentration
Neuropsychiatric	Wandering	Wanders during day/night
Cognitive Function	Cognition	Cognitive decline, mentally vague
Cognitive Function	Memory Loss	Memory loss, amnesia, poor memory
Cognitive Function	Confusion	Confusion, delirium, disorientated
Cognitive Function	Aphasia	Aphasia, speech therapy/defect, stammer
Daily Functioning	Bedbound	Bedbound, bed-ridden
Daily Functioning	Wheelchair	Provision of/independent in wheelchair

Daily Functioning	Severe mobility limitation	Housebound, chairbound, zimmer frame
Daily Functioning	Mobility – Less Severe Limitation	Mobility poor, walking stick, gait abnormality
Daily Functioning	Pressure Sore	Pressure sore, decubitus ulcer
Daily Functioning	Driving	Unfit to drive, advised about driving
Daily Functioning	Difficulty in Eating	Eating problem, dependent for eating
Daily Functioning	Difficulty Handling Finance	Needs help handling financial affairs
Daily Functioning	Personal Care Limitation	Dependent for dressing/toilet/bathing
Daily Functioning	Stairs Limitation	Difficulty managing stairs, need help on stairs
Safety	Fall	Recorded fall
Safety	Fracture	Recorded fracture (excl. skull)
Safety	Intracranial Injury	Skull fracture, concussion
Safety	Safety Assessment	Falls risk assessment, home safety advice
Comorbidity	Cardiovascular	Myocardial infarction, ischaemic heart disease
Comorbidity	Stroke	Stroke, cerebral infarction
Comorbidity	Parkinson's Disease	Parkinson's disease
Comorbidity	Motor Neurone Disease	Motor Neurone disease
Comorbidity	Diabetes	Diabetes mellitus (type I or II)
Comorbidity	Epilepsy	Epilepsy, grand mal/petiti mal, fit frequency
Comorbidity	Asthma / COPD	Asthma, COPD, chronic bronchitis
Comorbidity	Musculoskeletal Pain	Osteoarthritis, regional pain, rheumatoid arthritis
Comorbidity	Anaemia	Iron deficiency anaemia, Vitamin B12 deficiency
Comorbidity	Ocular	Cataract, retinopathy, glaucoma, blindness
Comorbidity	Hypertension	Essential hypertension, hypertensive disease
Comorbidity	Candidiasis	Candidiasis, thrush
Symptoms	Dizziness	Dizziness, vertigo, hypotension, giddiness
Symptoms	Incontinence	Incontinent of urine/faeces, urgency micturition
Symptoms	Constipation / IBS	Constipation, irritable bowel syndrome (IBS)
Symptoms	Diarrhoea	Diarrhoea, loose stools
Symptoms	Urinary	Retention of urine, haematuria, dysuria
Symptoms	Neurological	Fit (no epilepsy record), blackout
Symptoms	Chest Pain (non-cardiovascular)	Costochondritis, unspecified chest pain

Symptoms	Oral Health	Stomatitis, poor oral hygiene, sore mouth
Symptoms	Swallowing	Difficulty swallowing liquids/solids, dysphagia
Symptoms	Hearing Loss	Deafness, hearing loss/impairment
Symptoms	“Feels Unwell”	Recorded ‘Feels unwell’
Diet/Nutrition	Poor Diet	Advice re diet, high fat diet, dietician referral
Diet/Nutrition	Nutrition	Vitamin/iron deficiency, osteomalacia
Diet/Nutrition	Weight Loss	Weight decreasing/loss, underweight
Diet/Nutrition	Dietary Supplement	Dietary supplement
Imaging	Imaging	X-ray, MRI, ECG, DXA, angiogram, CAT scan
Increased Multimorbidity	Increase in Polypharmacy	Increase in count of different drugs prescribed
Dementia-related Drug	Change in Dementia-related Drug	New or changed dementia drug prescribed

Reproduced with permission (*to be obtained*) from Campbell et al., 2020¹⁰

© <year>, <Taylor & Francis / Imprint / Societies / Author>

Example, Copyright © 2012 Taylor & Francis Group

Table 2. Characteristics of patients with dementia, $n=30,463$

		n (% ^a)
Age:	Mean (SD)	81.6 (7.86)
Gender:	Male	11,132 (36.5)
	Female	19,331 (63.5)
Dementia type:	Alzheimer's	10,399 (34.1)
	Vascular	7,536 (24.7)
	Lewy Body	478 (1.6)
	Parkinson's	262 (0.9)
	Frontotemporal	48 (0.2)
	Not recorded or multiple types recorded	11,740 (38.5)
Body mass index:	Normal	11,044 (36.3)
	Overweight	7,100 (23.3)
	Obese	3,373 (11.1)
	Not recorded	8,946 (29.4)
Smoking status:	Non-smoker	13,888 (45.6)
	Current smoker	3,042 (10.0)
	Ex-smoker	8,493 (27.9)
	Not recorded	5,040 (16.5)
Alcohol consumption:	Non-drinker	4,743 (15.6)
	Current drinker	11,712 (38.5)
	Ex-drinker	987 (3.2)
	Not recorded	13,021 (42.7)
Year of dementia diagnosis:	1998-2009	15,340 (50.4)
	2010-2017	15,123 (49.6)
Geographical region:	North East	718 (2.4)
	North West	5,167 (17.0)
	Yorkshire & The Humber	1,191 (3.9)
	East Midlands	751 (2.5)
	West Midlands	3,958 (13.0)
	East of England	3,287 (10.8)
	South West	4,133 (13.6)
	South Central	4,079 (13.4)

	London	2,954 (9.7)
	South East Coast	4,225 (13.9)
Deprivation:	1 Least deprived	6,875 (22.6)
	2	6,817 (22.4)
	3	6,568 (21.6)
	4	5,601 (18.4)
	5 Most deprived	4,585 (15.1)

^a unless otherwise stated

Table 3. Prevalence and incidence of recorded domains

Domain	Prevalence in 24m before index date	Incidence ^a per 1000 person-years in 36m after index date	
	<i>n</i> (%)	<i>n^b</i> (%)	Incidence (95% CI)
Care	1,432 (4.7)	5,567 (19.1)	88.17 (85.89, 90.52)
Home Pressures	1,178 (3.9)	775 (2.7)	11.24 (10.48, 12.06)
Severe Neuropsychiatric	3,145 (10.3)	5,068 (18.6)	85.64 (83.31, 88.03)
Neuropsychiatric	13,834 (45.4)	5,922 (35.6)	186.36 (181.68, 191.17)
Cognitive Function	18,979 (62.3)	3,099 (27.0)	136.78 (132.05, 141.68)
Daily Functioning	2,558 (8.4)	4,684 (16.8)	76.45 (74.30, 78.68)
Safety	7,177 (23.6)	6,617 (28.4)	137.93 (134.65, 141.29)
Comorbidity	20,555 (67.5)	4,919 (49.7)	299.93 (291.67, 308.43)
Diet/Nutrition	5,388 (17.7)	5,971 (23.8)	112.41 (109.59, 115.29)
Symptoms	13,921 (45.7)	6,933 (41.9)	230.47 (225.11, 235.96)
Imaging	14,659 (48.1)	5,481 (34.7)	185.56 (180.72, 190.54)
Increased Multimorbidity	12,501 (41.0)	13,696 (76.3)	468.54 (460.76, 476.45)
Dementia-related Drug	1,623 (5.3)	10,335 (35.8)	206.65 (202.71, 210.67)

^a Incidence defined as first record of any marker within domain, in those with no marker from that domain recorded in 24m prior to index date; ^b in those with no record of domain in 24m before index date

Table 4. Associations of recording of domains with hospital admission, palliative care, and mortality

Domain	Hospital Admission			Palliative care			Mortality		
	<i>n</i> ^a	<i>n</i> (%) with outcome	HR ^b (95% CI)	<i>n</i> ^a	<i>n</i> (%) with outcome	HR ^b (95% CI)	<i>n</i> ^a	<i>n</i> (%) with outcome	HR ^b (95% CI)
Care	4,605	2,684 (58)	1.06 (1.02, 1.11)	6,539	684 (10)	1.64 (1.50, 1.80)	6,999	2,496 (36)	1.63 (1.56, 1.70)
Home Pressures	1,677	1,196 (71)	1.04 (0.97, 1.10)	1,929	171 (9)	1.23 (1.05, 1.43)	1,953	621 (32)	0.98 (0.91, 1.05)
Severe Neuropsychiatric	6,006	4,415 (74)	1.26 (1.21, 1.31)	7,890	729 (9)	2.23 (2.05, 2.44)	8,213	4,292 (52)	2.50 (2.41, 2.59)
Neuropsychiatric	17,511	12,995 (74)	1.25 (1.22, 1.29)	19,500	1,789 (9)	1.78 (1.63, 1.93)	19,756	7,984 (40)	1.73 (1.67, 1.79)
Cognitive Function	20,895	15,359 (74)	0.94 (0.91, 0.97)	21,891	1,916 (9)	1.04 (0.95, 1.13)	22,078	7,829 (35)	0.95 (0.92, 0.99)
Daily Functioning	5,018	3,632 (72)	1.26 (1.21, 1.31)	7,043	759 (11)	1.97 (1.81, 2.14)	7,242	3,441 (48)	1.92 (1.85, 1.98)
Safety	10,322	7,780 (75)	1.40 (1.35, 1.44)	13,596	1,275 (9)	1.67 (1.55, 1.81)	13,794	5,894 (43)	1.73 (1.68, 1.79)
Comorbidity	23,823	17,976 (75)	1.37 (1.33, 1.42)	25,255	2,249 (9)	1.60 (1.44, 1.79)	25,474	9,724 (38)	1.41 (1.35, 1.47)
Diet/Nutrition	8,440	5,913 (70)	1.15 (1.12, 1.19)	11,048	1,228 (11)	2.05 (1.90, 2.21)	11,359	5,090 (45)	2.02 (1.95, 2.09)
Symptoms	18,301	13,824 (76)	1.36 (1.32, 1.40)	20,627	1,940 (9)	1.82 (1.67, 1.99)	20,854	8,343 (40)	1.63 (1.57, 1.69)
Imaging	17,920	13,369 (75)	1.26 (1.23, 1.30)	19,934	1,833 (9)	1.30 (1.20, 1.42)	20,140	7,316 (36)	1.19 (1.15, 1.23)
Increased Multimorbidity	19,165	13,419 (70)	1.01 (0.99, 1.04)	24,675	2,111 (9)	2.01 (1.82, 2.21)	25,048	9,887 (39)	2.84 (2.70, 2.98)
Dementia-related Drug	9,821	6,329 (64)	0.85 (0.83, 0.88)	11,849	927 (8)	0.91 (0.84, 0.99)	11,958	3,471 (29)	0.93 (0.89, 0.96)

^a number with recorded marker from domain in 24m before index to earliest of outcome or 36m after index date; ^b reference is those with no marker from domain; HR is adjusted for age and gender

Table 5. Association of the cumulative number of domains with new recorded markers in the first year after diagnosis with hospital admission, palliative care, and mortality after the first year

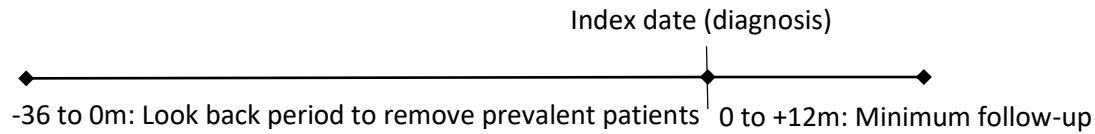
Number of domains	Number of patients	<i>n</i> (%) with outcome	Unadjusted HR (95% CI)	Adjusted HR ^a (95% CI)
Hospital admission ^b				
0	3,540	2,216 (62.6)	1.00	1.00
1	5,702	3,350 (58.8)	0.99 (0.94, 1.05)	1.03 (0.97, 1.08)
2	4,672	2,797 (59.9)	1.06 (1.00, 1.13)	1.09 (1.03, 1.16)
3	2,838	1,711 (60.3)	1.13 (1.05, 1.22)	1.16 (1.07, 1.25)
4+	2,353	1,375 (58.4)	1.20 (1.12, 1.29)	1.24 (1.15, 1.33)
Palliative care ^c				
0	4,353	285 (6.6)	1.00	1.00
1	7,725	528 (6.8)	1.14 (0.99, 1.31)	1.11 (0.96, 1.28)
2	7,243	554 (7.6)	1.31 (1.14, 1.51)	1.28 (1.11, 1.47)
3	5,152	410 (7.0)	1.48 (1.25, 1.74)	1.44 (1.22, 1.69)
4+	5,411	502 (9.3)	1.96 (1.70, 2.26)	1.87 (1.62, 2.15)
Mortality				
0	4,408	1,632 (37.0)	1.00	1.00
1	7,839	2,731 (34.8)	1.01 (0.96, 1.07)	1.05 (0.99, 1.11)
2	7,369	2,731 (37.1)	1.11 (1.05, 1.18)	1.16 (1.09, 1.23)
3	5,253	2,040 (38.8)	1.24 (1.16, 1.33)	1.26 (1.18, 1.36)

4+	5,594	2,394 (42.8)	1.56 (1.46, 1.67)	1.57 (1.47, 1.67)
----	-------	--------------	-------------------	-------------------

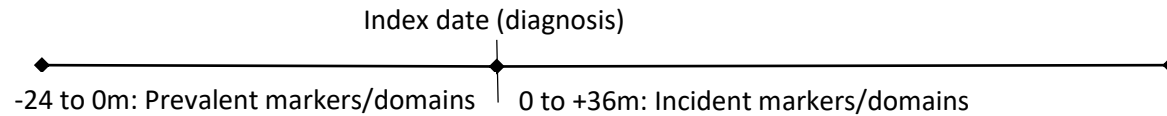
^a HR adjusted for age, gender, BMI, smoking status, alcohol consumption, deprivation, year of index date, and geographical region; ^b Excludes those with record of hospitalisation in the 12 months after index date; ^c Excludes those with record of palliative care in 24 months before index date or in the 12 months after index date

Figure 1. Time windows for the study

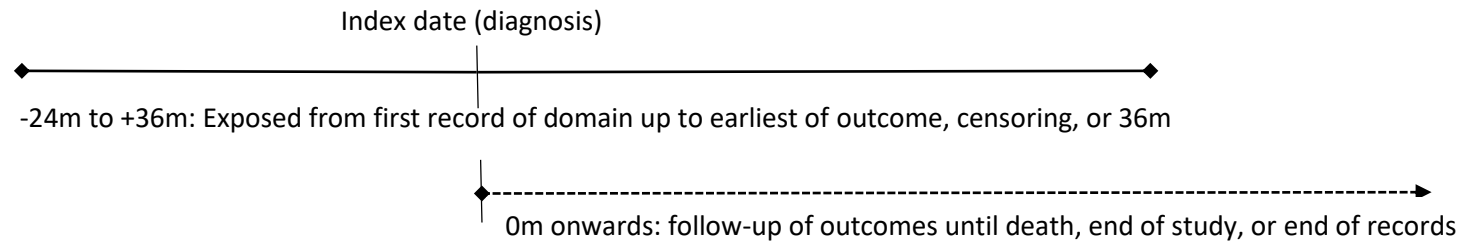
1a) Study population definitions



1b) Prevalence and incidence of markers and domains



1c) Association of individual domains with outcomes



1d) Association of accumulation of markers post-diagnosis with outcomes

