ISAC Approved protocol: No. 15-148

Longitudinal Analyses of Blood Lipids and Future Risk of Dementia in CPRD

Principal Investigator:
Nawab Qizilbash MRCP MSc DPhil
Senior Clinical Epidemiologist, OXON Epidemiology, Spain
and Honorary Associate Professor in Pharmacoepidemiology, London School of Hygiene & Tropical Medicine.
Email: n.qizilbash@oxonepi.com

Co-Investigators:
John Gregson PhD[1], Kevin Wing PhD[1], Michelle Johnson[2], Ian Douglas PhD[1], Neil Pearce PhD[1], Stephen Evans MSc[1], Stuart Pocock PhD[1]

[1]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK.
[2]OXON Epidemiology, London, UK

Longitudinal Analyses of Blood Lipids and Future Risk of Dementia in CPRD

Nawab Qizilbash
John Gregson
Michelle Johnson
Kevin Wing
Ian Douglas
Neil Pearce
Stephen Evans
Stuart Pocock

London School of Hygiene & Tropical Medicine

SUMMARY OF RESEARCH

Dementia prevalence is increasing and represents a major burden for health and social services. Establishing modifiable risk factors of dementia risk is a national and global priority. The relationship of blood lipids to the risk of developing dementia is unclear. Previous research based on small studies suggests that people who have raised lipids in midlife may have a higher chance of developing dementia some 20 years later than people with lower blood lipid levels. The proposed study will use information from a large number of people in the UK to investigate the relationship between lipids and the future risk of developing dementia. People aged 40 years or older with a blood lipid reading between 1992 and 2009 will be selected from the CPRD primary care database. Their recorded development of dementia will be investigated, whilst accounting for differences in characteristics (e.g. age, gender, etc.). This study will provide information from a very large number of people with a sizeable amount of follow-up data which will be representative of the UK population. The findings will therefore provide important information to help clarify the relationship between blood lipids and dementia. The findings will help to inform preventative strategies for dementia.

OBJECTIVES AND RATIONALE

The primary objectives of the analysis are to:

1. Estimate the association between blood total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), non-HDL cholesterol (NHDL) and TC/HDL and future risk of dementia
2. Estimate the age-specific associations between TC, HDL, LDL, NHDL and TC/HDL and dementia

Secondary aims are to:

1. Assess the shape of the associations and identify any deviation from a linear relationship.
2. Identify potential modifiers and confounders of the risk, particularly: myocardial infarction (MI), stroke, diabetes mellitus, body mass index (BMI), cigarette smoking

and alcohol consumption, use of lipid lowering agents (statins, fibrates, nicotinic acid, bile acid resins) and anti-hypertensive drugs.

By conducting these analyses, we will provide precise results which will clarify the conflicting evidence, be usable for disease prediction models, patient management, the planning of trials, and support (or refute) hypotheses of pathophysiological mechanisms relating lipids with potential modifiers to the development of dementia.

BACKGROUND

The prevalence of dementia is expected to increase by 400% over the next 20 years due to the ageing population (1). The prevalence of total cholesterol levels above 5 mmol/l remains high in England with 56% of men and 57% of women (2); the maximum level suggested for those with vascular disease, diabetes or hypertension who are on drug treatment.

Predictive scores have been developed of future dementia risk based on midlife hyperchlosterolaemia, among other modifiable risk factors (3). This risk score assesses the dementia risk 20 years later in middle–aged people; the elements are hypercholesterolaemia , hypertension, obesity, low education and age ≥ 47 within the middle-age range (3). Meanwhile, a United States NIH National Institutes of Health State-of-the-Science Conference independent panel concluded in 2011 that that there is currently, insufficient evidence to draw firm conclusions on the association (4).

Conflicting findings have obscured defining a precise relationship between lipids and dementia. Most studies do not show a statistically significant increase in dementia risk from higher TC and some indicate a lower risk (5,6). In those which are statistically significant, the lower confidence interval is very close to unity, indicating poor precision and results that are vulnerable to modest bias. The variety of results may partly have arisen as some studies analysed TC as a categorical variable and others per 1 mmol/l or standard deviation increase. Also, there was variation in the adjustment for important confounding variables such as medical history, smoking, alcohol, blood pressure (BP), BMI and race, and variation in the adjustment for competing risks of mortality (6–13). Most of the cohort studies had limited power due to relatively small samples and varying durations of follow-up and not allowing for reverse causation due to pre-existing disease. Some studies suggest that low HDL may be associated with higher risk of dementia (11) and high LDL and increased risk of dementia (7) while one study indicated that higher NHDL was associated with a lower risk of dementia (6).

If the association between lipids and dementia were to be confirmed, it cannot be assumed that the risks of dementia from lipid levels are similar in different age groups. Indeed, studies of TC, LDL and HDL and the well-established risks of myocardial infarction (MI), in sufficiently large cohorts or meta-analyses of cohort studies, suggest that this is unlikely to be true (14). Furthermore, ischaemic stroke mortality and total stroke mortality have been positively associated with TC only in middle age (40-69 years) and only in those with lower blood pressure (14) while at older ages or at higher blood pressure levels, TC is not positively associated with ischaemic stroke mortality (14). The consequences of differing risks by age may have direct implications for patient management, e.g. the need, or otherwise, for differing degrees of lowering TC and LDL and raising HDL in the very elderly for the reduction in risk of dementia.

The mechanisms for how increased TC, LDL and reduced HDL may lead to dementia are unknown but may include mechanism related to intracranial atherosclerosis which may operate independently of Alzheimer's pathology or cerebral infarcts (15).

As LDL is often calculated from directly assayed TC and directly assayed HDL, NHDL will also be used as a measure of LDL and will be used in joint analyses with other lipid variables (i.e. HDL and TC) (14). We will also collect triglyceride levels, where available, in order to use the more accurate Friedwald formula to calculate LDL: LDL-cholesterol (in mmol/L) = total cholesterol—[HDL-cholesterol + (triglycerides/2.17)].

The proposed study will establish or refute the relationship between the level of lipids (TC, HDL, LDL, NHDL and TC/HDL ratio) and future dementia, with large numbers of people followed for over 20 years and many thousands of people with the endpoint of dementia. It will also describe precisely how the association varies with age and time and whether the relationship is linear throughout the range or whether any thresholds exist. Furthermore, it will adjust for known confounding factors for dementia, such as MI, stroke, diabetes, smoking, and other speculative factors associated with dementia such as BMI (16), alcohol, statins and antihypertensive drugs. A recent study in Clinical Practice Research Datalink (CPRD) has seriously contradicted previous conflicting research of the relationship of BMI with dementia (16), and which subsequently have been supported by three smaller studies reported as letters to the Lancet Diabetes & Endocrinology.

The CPRD general practice database has many thousands of cases recorded with a diagnosis of dementia, and with the use of TC, HDL, LDL, NHDL and TC/HDL as continuous variables on many thousands of people followed at varying lengths for over 20 years should provide extremely precise estimates to detect and characterise an association and produce valuable new information.

Dementia has been validated as a diagnosis in CPRD and analyses of drugs and dementia in CPRD have been published in a number of leading journals (17,18). A recent analysis of BMI and dementia risk from CPRD was published in Lancet Diabetes and Endocrinology; this study will use a similar approach to assess the association between lipids (TC, HDL, LDL, NHDL) and future risk of dementia (16).

METHODOLOGY

Study type: *Descriptive study*

Study design: A retrospective dynamic cohort design will be employed for patients identified from the CPRD UK primary care database

Study population:

Cohort inclusion. The analysis will include all patients with at least one record of a lipid value (1.75<TC(mmol/l)<20 or 65<TC(mg/dl)<775; 0.25<HDL(mmol/l)<3.25 or 10<HDL(mg/dl)<120; 0.75<LDL(mmol/l)<8.0 or 30<LDL(mg/dl)<300 (19)) and who were aged 40 years or older between 1st January 1992 and 31st December 2009. 1st January 1992 is the date from which practices began to be documented as being 'up-to-standard' in terms of data collection and audit in the database. Use of only data from practices that were deemed to be providing data in the manner required by the database provider increases the validity of the data used for this analysis. Start of follow-up will be from the time of the first eligible lipid reading (after 'up-to-standard' date [date at which a practice was considered to be providing data of

adequate quality] and with one year of data prior to the date of patients' lipid reading). Follow-up (censoring) for each patient will end at the earliest of the date of the practice's last CPRD data collection, the end of the patient's record collection (due to death or leaving the practice) and the date of the first record of dementia.

A separate 10% random sample of people without lipid readings (and without a diagnosis of dyslipidaemia, hyperlipidaemia or hypercholesterolaemia) will also be selected to allow comparison with the lipid cohorts for the corresponding covariates.

Cohort exclusion Patients with a record of dementia prior to the first eligible lipid reading will be excluded in the analysis of dementia.

Sample size: This is an observational study and it is intended that all eligible patients selected from CPRD who meet the defined inclusion and exclusion criteria will be included for analysis. The sample will be large and more than adequate for the analyses. For example, there were over 45,000 incident patients in CPRD identified with dementia between 1992 and 2013 in a cohort of almost 2 million people followed up for up to 2 decades (16) and we anticipate at least 500,000 people with lipid values, given the attention lipid lowering has received over the last two decades. A study in CPRD found that lipid levels had been measured in approximately 55% of people in the year before the onset of a first stroke, and this population is likely to mirror our cohort, so we are confident that there will be at least 500,000, and very likely many more, with lipid recordings (24).

Depending on the assumptions, a sample size of greater than 500,000 patients will be able to detect a difference in the rate of dementia between two groups (e.g. low and high lipids) if there is a difference. Therefore, a sample of at least 500,000 patients will be selected.

Incidence rate per 1,000 patient-years	5	3	2.4*	1	2.4*	2.4*
Relative risk[#]	1.6	1.6	1.6	1.6	1.4	1.2
Confidence level	95%	95%	95%	95%	95%	95%
Power	90%	90%	90%	90%	90%	90%
Total sample size required	**30,148**	**50,384**	**63,032**	**151,568**	**130,956**	**480,310**

* Source: Qizilbash et al (16)

Source: Based on relative risk estimate ranges reported in several studies reviewed in Kloppenborg et al (5).

Outcome definition and measures: We will identify people in the cohort who have Read codes for the outcomes of interest in their computerised medical record: dementia. If required, patients with dementia will be further classified into Alzheimer's disease and vascular dementia using a validated algorithm (20). The code list and algorithm are included in the appendix.

Exposure definition and measures*:* The exposure will start at the first recorded eligible lipid reading.

Covariate definition and measures: Potential confounders and effect modifiers at or before the first eligible lipid reading for cohort inclusion for dementia will be coded and analysed, where available:

- Calendar year of first lipid recording
- Age at first lipid recording
- Age at first recording of dementia
- Sex
- Ethnicity (white, south Asian, Black, mixed, other)
- Socioeconomic deprivation (quintiles)
- BMI in kg/m^2 (<20, 20-24.9, 25-29.9, 30-34.9, 35-39.9, 40+)
- Systolic blood pressure (quintiles)
- Smoking (current, past, never, unknown)
- Alcohol (never drinker, ex-drinker, current drinker, unknown)
- Vascular disease (MI or stroke: yes, no)
- Diabetes mellitus (yes, no)
- Atrial fibrillation/flutter (yes, no)
- Heart failure (yes, no)
- Chronic obstructive pulmonary disease (yes, no)
- Drug prescription within an appropriate time window (e.g. 12 months) at or prior to the first lipid reading: lipid-lowering agents (statins, fibrates, nicotinic acid, bile acid resins) and anti-hypertensive drugs (thiazide diuretics, β blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers)

In addition, repeat recordings of lipids after the initial reading will be extracted for analysis to explore more complex time-relationships between lipids and dementia and to adjust for regression dilution bias.

Data collection and management: The data will be extracted from the CPRD database. CPRD contains computerised health care information from over 680 general practices since 1987 on over 15 million patients. However, auditing of the data collection from practices began in 1992. Two large validation studies determined that information on all patient referrals and hospitalisations was recorded on the computer over 90% of the time (21,22).

Validation procedures: The codes chosen to select the outcomes will seek to enhance specificity at the expense of sensitivity, as we will not validate the diagnosis by recourse to the original GP records. Validation of this data source has previously been conducted for a wide range of conditions (21,22) and specifically for dementia (17). The algorithm we will use for classifying Alzheimer's disease and vascular dementia has recently been validated (20).

Data analysis:
We will present the characteristics of the selected cohort. Similar to the methods conducted recently for an analysis of BMI and dementia (16), we will assess evidence of the association between lipids and future diagnosis of dementia using survival techniques:

- We will conduct Poisson regression analyses to estimate the magnitude of any associations between lipids and risk of dementia.
- We will assess incidence rates of dementia by appropriate baseline categories of TC (<4.5, 4.5-, 5.5-, 6.5-, 7.5-, ≥8.5 mmol/l), HDL (<1.0, 1.0-, 1.25-, ≥1.5 mmol/L), HDL

((4.0, 4.0-, 5.0-, ≥6.0 mmol/L), NHDL (4.0, 4.0-, 5.0-, ≥6.0 mmol/L) and baseline total/HDL (<4.25, 4.25-, 5.5-, ≥6.75 mmol/L), stratified by age and sex categories.

- Rates of dementia in the first year after the first lipid reading will be compared with rates in subsequent years (0-1 year, 1-5 years, 5-9 years, 10-15 years, 15+ year) and by calendar year.
- Specifically, rates of dementia by time since lipid measurement in those aged <55 at the time of lipid measurement by a period of follow-up of greater than 15 years will be analysed.
- Lipids will also be analysed as continuous variables.
- We will assess the role of covariates as potential confounders and effect modifiers. This will be done by including them as additional predictor variables in the Poisson regression model. Appropriate interaction terms with lipids will also be included to explore their role as potential effect modifiers. Particular covariates of interest include the following:
    - Calendar year (5 year intervals)
    - Age (40-49, 50-59, 60-69, 70-79, >= 80)
    - Sex (M, F)
    - Ethnicity (White, south Asian, Black, Mixed, other)
    - Socioeconomic deprivation in English practices only (quintiles)
    - BMI in kg/m^2 (<20, 20-24.9, 25-29.9, 30-34.9, 35-39.9, 40+)
    - Systolic BP (quintiles)
    - Smoking (current, past, never, unknown)
    - Alcohol (never drinker, ex-drinker, current drinker, unknown)
    - Vascular disease (MI or stroke: yes, no)
    - Diabetes mellitus (yes, no)
    - Atrial fibrillation/flutter (yes, no)
    - Heart failure (yes, no)
    - Chronic obstructive pulmonary disease (yes, no)
  - Drug prescription within an appropriate time window (e.g. 12 months) at or prior to the first lipid reading: lipid-lowering agents (statins, fibrates, nicotinic acid, bile acid resins) and anti-hypertensive drugs (thiazide diuretics, β blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers)
- Adjustment for regression dilution bias may be made.

We will present the characteristics of the selected non-lipid cohort and compare the lipid and non-lipid cohorts by baseline covariates.

The STATA statistical package will be used for analysis.

LIMITATIONS

The design described above has been performed on baseline BMI and dementia and total mortality, demonstrating the appropriateness of the design, data source and statistical analysis. Studies have been conducted successfully in dementia using this large primary care database (16–18, 20, 23). The analysis will advance substantially previous work and clarify the confusion because of its large size, long follow-up and widespread generalisability to the general population.

***Confounding*:** Several potential confounders will be controlled for but others such as exercise are not available and others with missing data may result in residual confounding.

Bias: Systematic bias from regression dilution (misclassification of the exposure from only one reading, operating in many protocol driven prospective cohort studies) may be corrected for in the analysis. Examination of dementia rates across calendar years will help to assess surveillance bias. Loss to follow-up will be examined (16). Competing risk of death will be allowed for in the analysis (16). Birth cohort effects will be examined (16).

Misclassification: The limited ability to distinguish reliably between subtypes of dementia may underestimate an association of lipids and dementia risk, if there is an association with only one major subtype of dementia. This may be explored with analyses of the two major types of dementias, Alzheimer's disease and vascular dementia. We will use a validated algorithm used in a recent study in CPRD (20) to identify the two major types of dementias described in the appendix. In 79% of Alzheimer's disease cases confirmation was obtained from the general practitioner and in 75% of vascular dementia cases.

Missing data*:* There may be missing data of variable magnitude for several covariates, such as ethnicity, BMI, smoking and alcohol. This may leave some residual confounding but again the nature of the dose-relationship of this analysis may help against these kind of missing data. We will conduct sensitivity analyses for those patients with complete covariate data to assess this source of potential bias. Imputation methods may be used depending on the pattern of missing data.

Reverse causation: We will assess potential reverse causation by examining dementia rates by time from the initial lipid recording.

Generalisibility: As lipids may have been selectively recorded, especially before 2004 when the Quality and Outcomes Framework was introduced in UK general practice, we will conduct analyses of lipids recordings before and after 2004 (16). We will conduct stratified analyses by certain baseline co-variates, such as MI, stroke, diabetes mellitus, SBP, BMI and statin use to assess the robustness of the associations as an indirect test of generalisability. We will also compare lipid levels with population surveys in the UK. A random sample pf people without lipid readings will be compared with the lipid cohort for baseline age, sex, ethnicity etc, to assess the degree of selectiveness of the lipid cohort.

PATIENT CONFIDENTIALITY

All data provided by the database provider (CPRD) are completely anonymised.

PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

It is intended that the results of the planned study will be used as a basis for presentations at international conferences and publication(s) in peer-reviewed journal(s). We adhere to the Guidelines for Good Pharmacoepidemiology Practices (http://www.pharmacoepi.org/resources/guidelines_08027.cfm) in order to help ensure the quality and integrity of pharmacoepidemiologic research and to provide adequate documentation of research methods and results. We adhere to international guidelines on authorship (http://www.icmje.org/ethical_1author.html).

REFERENCES

1. Brookmeyer R GS. Methods for projecting the incidence and prevalence of chronic diseases in aging populations: application to Alzheimer's disease. Stat Med. 2000;19:1481–93.

2. Health and Social Care Information Centre. Health, social care and lifestyles: Summary of key findings - Health Survey for England [Internet]. 2011. Available from: http://www.hscic.gov.uk/catalogue/PUB09300/HSE2011-Sum-bklet.pdf

3. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005;62(10):1556–60.

4. Daviglus ML, Plassman BL, Pirzada A, Bell CC, Bowen PE, Burke JR, et al. Risk factors and preventive interventions for Alzheimer disease: state of the science. Arch Neurol [Internet]. 2011 Sep [cited 2015 May 25];68(9):1185–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21555601

5. Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. Eur J Pharmacol [Internet]. 2008 May 6 [cited 2015 May 25];585(1):97–108. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18395201

6. Batty GD, Russ TC, Starr JM, Stamatakis E, Kivimäki M. Modifiable cardiovascular disease risk factors as predictors of dementia death: pooling of ten general population-based cohort studies. J Negat Results Biomed [Internet]. 2014 Jan [cited 2015 Jun 3];13(1):8. Available from: http://www.jnrbm.com/content/13/1/8

7. Hall K, Murrell J, Ogunniyi A, Deeg M, Baiyewu O, Gao S, et al. Cholesterol, APOE genotype, and Alzheimer disease: an epidemiologic study of Nigerian Yoruba. Neurology [Internet]. 2006 Jan 24 [cited 2015 Jun 19];66(2):223–7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2860622&tool=pmcentrez&rendertype=abstract

8. Kivipelto M, Helkala E-L, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, et al. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med [Internet]. 2002 Aug 6 [cited 2015 Jun 19];137(3):149–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12160362

9. Li G, Shofer JB, Kukull WA, Peskind ER, Tsuang DW, Breitner JCS, et al. Serum cholesterol and risk of Alzheimer disease: a community-based cohort study. Neurology [Internet]. 2005 Oct 11 [cited 2015 Jun 19];65(7):1045–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16217057

10. Mielke MM, Zandi PP, Sjögren M, Gustafson D, Ostling S, Steen B, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology [Internet]. 2005 May 24 [cited 2015 Jun 16];64(10):1689–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15911792

11. Reitz C, Tang M-X, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol [Internet]. 2004 May [cited 2015 Jun 19];61(5):705–14. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2696387&tool=pmcentrez&rendertype=abstract

12. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology [Internet]. 2005 Jan 25 [cited 2015 May 20];64(2):277–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15668425

13. Solfrizzi V, Panza F, Colacicco AM, D'Introno A, Capurso C, Torres F, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology [Internet]. 2004 Nov 23 [cited 2015 May 21];63(10):1882–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15557506

14. Prospectice Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet [Internet]. 2007 Dec 1 [cited 2015 Feb 1];370(9602):1829–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18061058

15. Evidence based Dementia Practice - Nawab Qizilbash, Lon S. Schneider, Henry Brodaty, et al [Internet]. [cited 2015 May 25]. Available from: http://eu.wiley.com/WileyCDA/WileyTitle/productCd-0632052961.html

16. Qizilbash N, Gregson J, Johnson ME, Pearce N, Douglas I, Wing K, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. Lancet Diabetes Endocrinol [Internet]. Elsevier; [cited 2015 Apr 10]; Available from: http://www.thelancet.com/article/S2213858715000339/fulltext

17. Seshadri S, Zornberg GL, Derby LE, Myers MW, Jick H, Drachman DA. Postmenopausal estrogen replacement therapy and the risk of Alzheimer disease. Arch Neurol [Internet]. 2001 Mar [cited 2015 Jan 26];58(3):435–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11255447

18. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. Lancet [Internet]. 2000 Nov 11 [cited 2015 Mar 9];356(9242):1627–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11089820

19. Littman A, Boyko E, McDonell M, Fihn S. Evaluation of a Weight Management Program for Veterans. Prev Chronic Dis [Internet]. 2012 May [cited 2015 May 25];9. Available from: http://www.cdc.gov/pcd/issues/2012/11_0267.htm

20. Imfeld P, Brauchli Pernus YB, Jick SS, Meier CR. Epidemiology, Co-Morbidities, and Medication Use of Patients with Alzheimer's Disease or Vascular Dementia in the UK. J Alzheimers Dis. 2013;35(3):565–73.

21. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ. 1991;302(6779):766–8.

22. Jick H, Terris BZ, Derby LE JS. Further validation of information recorded on a general practitioner based computerised data resource in the United Kingdom. Pharmacoepidemiol Drug Saf. 1992;1:347–9.

23. Laredo L, Vargas E, Blasco AJ, Aguilar MD, Moreno A, Portolés A. Risk of cerebrovascular accident associated with use of antipsychotics: population-based case-control study. J Am Geriatr Soc. 2011 Jul;59:1182–7.

24. Dregan A, Toschke MA, Wolfe CD, Rudd A, Ashworth M, Gulliford MC; eCRT Research team. Utility of electronic patient records in primary care for stroke secondary prevention trials. BMC Public Health. 2011 Feb 7;11:86.

APPENDIX

Code list: dementia

Read code	Description
e00..12	senile/presenile dementia
f110.00	alzheimer's disease
eu01.00	[x]vascular dementia
eu02z00	[x] unspecified dementia
e00..11	senile dementia
e000.00	uncomplicated senile dementia
eu00.00	[x]dementia in alzheimer's disease
1461	h/o: dementia
eu02z14	[x] senile dementia nos
eu00z11	[x]alzheimer's dementia unspec
e004.11	multi infarct dementia
e004.00	arteriosclerotic dementia
eu02500	[x]lewy body dementia
e001.00	presenile dementia
f116.00	lewy body disease
eu02300	[x]dementia in parkinson's disease
e041.00	dementia in conditions ec
eu00112	[x]senile dementia,alzheimer's type
eu01100	[x]multi-infarct dementia
eu01.11	[x]arteriosclerotic dementia
eu00200	[x]dementia in alzheimer's dis, atypical or mixed type
eu00z00	[x]dementia in alzheimer's disease, unspecified
e012.11	alcoholic dementia nos
e002100	senile dementia with depression
f110100	alzheimer's disease with late onset
eu02.00	[x]dementia in other diseases classified elsewhere
eu01z00	[x]vascular dementia, unspecified
f110000	alzheimer's disease with early onset
e002000	senile dementia with paranoia
eu00100	[x]dementia in alzheimer's disease with late onset
eu10711	[x]alcoholic dementia nos
eu01300	[x]mixed cortical and subcortical vascular dementia
f111.00	pick's disease
e003.00	senile dementia with delirium
e004z00	arteriosclerotic dementia nos
e002.00	senile dementia with depressive or paranoid features
eu00000	[x]dementia in alzheimer's disease with early onset
e001z00	presenile dementia nos
eu02z16	[x] senile dementia, depressed or paranoid type
eu02200	[x]dementia in huntington's disease

Read code	Description
eu01200	[x]subcortical vascular dementia
e001200	presenile dementia with paranoia
eu02000	[x]dementia in pick's disease
eu01y00	[x]other vascular dementia
e004000	uncomplicated arteriosclerotic dementia
e001300	presenile dementia with depression
eu02z13	[x] primary degenerative dementia nos
e012.00	other alcoholic dementia
e004300	arteriosclerotic dementia with depression
eu00113	[x]primary degen dementia of alzheimer's type, senile onset
eu02z11	[x] presenile dementia nos
e001100	presenile dementia with delirium
eu04100	[x]delirium superimposed on dementia
eu02100	[x]dementia in creutzfeldt-jakob disease
eu00011	[x]presenile dementia,alzheimer's type
eu02y00	[x]dementia in other specified diseases classif elsewhere
eu01000	[x]vascular dementia of acute onset
e004200	arteriosclerotic dementia with paranoia
e002z00	senile dementia with depressive or paranoid features nos
e001000	uncomplicated presenile dementia
eu01111	[x]predominantly cortical dementia
eu00111	[x]alzheimer's disease type 1
e02y100	drug-induced dementia
eu02400	[x]dementia in human immunodef virus [hiv] disease
e004100	arteriosclerotic dementia with delirium
eu00012	[x]primary degen dementia, alzheimer's type, presenile onset
eu00013	[x]alzheimer's disease type 2
fyu3000	[x]other alzheimer's disease

Identification of Alzheimer's disease requires one of the following (20)**:**

- A diagnosis of Alzheimer's disease followed by at least one prescription for an Alzheimer's disease drug or vice versa;
- A diagnosis of unspecific dementia followed by at least two prescriptions for an Alzheimer's disease drug or vice versa;
- At least two recordings of an Alzheimer's disease diagnosis
- A diagnosis of Alzheimer's disease after a specific dementia test, a referral to a specialist, or an assessment based on neuroimaging
- A diagnosis of Alzheimer's disease preceded or followed by any recorded dementia symptoms

AND exclusion of:

- Alzheimer's disease with a recording of any other specific dementia
- Alzheimer's disease with a recording of stroke within two years prior to the date of the Alzheimer's disease

Identification of vascular dementia requires one of the following (20)**:**

- A diagnosis of vascular dementia or unspecific dementia within two years of a stroke
- At least two recordings of an vascular dementia diagnosis
- A diagnosis of vascular dementia after a specific dementia test, a referral to a specialist, or an assessment based on neuroimaging
- A diagnosis of vascular dementia preceded or followed by any recorded dementia symptoms

AND exclusion of:

- Vascular dementia with a recording of any other specific dementia
- Vascular dementia with a prescription of a specific drug for Alzheimer's disease