Title

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Journal

The Journal of Prevention of Alzheimer's Disease, 1(2)

ISSN

2274-5807

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Publication Date

2014-02-01

DOI

10.14283/jpad.2014.35

Peer reviewed

HHS Public Access

Author manuscript

J Prev Alzheimers Dis. Author manuscript; available in PMC 2015 July 01.

Published in final edited form as:

J Prev Alzheimers Dis. 2014 February ; 1(2): 117–123.

Dementia Prevention: optimizing the use of observational data for personal, clinical, and public health decision-making

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Abstract

Worldwide, over 35 million people suffer from Alzheimer's disease and related dementias. This number is expected to triple over the next 40 years. How can we improve the evidence supporting strategies to reduce the rate of dementia in future generations? The risk of dementia is likely influenced by modifiable factors such as exercise, cognitive activity, and the clinical management of diabetes and hypertension. However, the quality of evidence is limited and it remains unclear whether specific interventions to reduce these modifiable risk factors can, in turn, reduce the risk of dementia. Although randomized controlled trials are the gold-standard for causality, the majority of evidence for long-term dementia prevention derives from, and will likely continue to derive from, observational studies. Although observational research has some unavoidable

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limitations, its utility for dementia prevention might be improved by, for example, better distinction between confirmatory and exploratory research, higher reporting standards, investment in effectiveness research enabled by increased data-pooling, and standardized exposure and outcome measures. Informed decision-making by the general public on low-risk health choices that could have broad potential benefits could be enabled by internet-based tools and decision-aids to communicate the evidence, its quality, and the estimated magnitude of effect.

Keywords

Alzheimer's; primary prevention; non-randomized studies; low-risk; communication

Introduction

Alzheimer's disease and other age-related dementias (referred to here for simplicity as "dementia") afflict over 35 million people world-wide. The societal cost of care in 2010 was estimated at over $600 billion, 1% of the world's aggregated gross domestic product, with 89% of those costs incurred by high-income countries [1].

Mounting evidence suggests that modifiable factors in mid-life will alter an individual's risk of dementia in later decades. For example, one analysis concluded that almost half the statistical probability of getting Alzheimer's disease may be accounted for by seven modifiable risk factors – diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity or low educational attainment, and physical inactivity – and reducing the prevalence of these risk factors by 10% could prevent up to 1.1 million cases of the disease worldwide [2]. Another analysis estimated that a 10% reduction in body mass index among overweight or obese beneficiaries would save Medicare and Medicaid $6 billion and $35 billion, respectively, from the cost of dementia over the lifetime of baby boomers[3].

Analyses like these provide a compelling rationale to invest in further research about preventing dementia through lifestyle changes, non-pharmaceutical interventions, and the management of other health risks particularly in midlife. However, the current evidence has major limitations that led the NIH State-of-Science Report on Preventing Alzheimer's Disease and Cognitive Decline to conclude that there are no preventive interventions currently available. First, most of the available evidence has focused on identifying risk factors rather than the effectiveness of specific actions to modify those risk factors. Second, the evidence derives almost entirely from observational research of quality that varies and is often difficult to assess.

How can we optimize the existing data particularly for low-risk long-term interventions on modifiable risk factors? Meta-analyses of randomized controlled trials currently are viewed to provide the highest level of evidence for causal inference and intervention efficacy. However, sole dependence on randomized controlled trials is not a feasible solution[4]. While observational studies have inherent limitations, they can provide evidence complementary to RCTs. The goal of this paper is to recommend strategies to maximize the utility of observational data for low-risk health choices that may protect against dementia.

Why RCTs will not be the only source of evidence for dementia prevention interventions

Randomized controlled trials are the gold standard to quantify causal inference but they are few and far between for dementia prevention, particularly for primary prevention before the disease takes hold in the brain. Alzheimer's and several related causes of dementia likely begin in the brain decades before the appearance of clinical symptoms. Although biomarkers have been proposed, none have yet been validated as diagnostic or as an efficacy surrogate, so proof of primary prevention requires studying a treatment that begins and continues for years if not decades before clinical symptoms manifest. For these reasons, randomized trials have typically been of insufficient duration and power to detect the effectiveness of primary prevention interventions[5].

In recent years, collaborative initiatives have improved the design and feasibility of randomized trials for Alzheimer's prevention, particularly secondary prevention in asymptomatic but high-risk populations in whom the disease has likely initiated in the brain but has not yet manifested in clinical symptoms[5; 6; 7; 8; 9]. Additional outcomes relevant to dementia might be added into large RCTs designed to answer different research questions, as occurred with the PREADVISE trial that added memory loss and dementia prevention outcomes to a trial for cancer prevention with selenium and vitamin E (NCT00040378). Randomized trials of drugs, nutrition, vitamin supplementation, or exercise originally designed for cardiovascular or diabetes indications may be re-repurposed years later, linking participant IDs with routinely available data from medical records or other sources to obtain long-term follow-up and outcome measures relevant to dementia.

Despite these important advances, randomized trials are unlikely the sole and sufficient solution to answer many questions about low-risk and long-term prevention strategies. Randomized trials of sufficient duration often have restrictive eligibility criteria that prevent the trial results from being generalized with confidence to other groups of adults[4; 5]. Non-pharmaceutical strategies to reduce dementia like behavior change, nutrition, and health management typically have limited commercial value, so the research must generally be funded by government agencies or philanthropy. RCTs are extremely expensive; however, trials necessary to test non-pharmaceutical prevention strategies will likely require long-term multi-domain interventions, increasing the time and money required to detect benefit. In the meantime, our population continues to age and the critical windows to intervene and prevent dementia may be closing for many individuals.

Maximize the utility of observational data

Evidence-based medicine has been defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients"[10]. It requires careful analysis of the available high-quality research on population samples to inform decisions for individual patients. Major evidence-based medicine groups like GRADE, Cochrane, and AHRQ agree that although double-blind randomized controlled trials are the gold-standard for causality, observational studies can sometimes be considered

as moderate or even strong evidence[11] that may be included in systematic reviews [12; 13]. In practice, however, observational studies rarely achieve that status.

Observational studies have inherent limitations, particularly for causal inference, that cannot be easily overcome. The risk of confounding and other biases can be reduced but never eliminated by statistical adjustments. Because observational studies are typically less well-resourced, they can also be undermined to a greater extent than RCTs by other biases that may not be taken into account. However, sole dependence on randomized controlled trials is not a feasible solution [4], particularly for long-term and low-risk non-pharmaceutical interventions. The goal of this paper is to recommend six strategies to maximize the utility of observational data to support decision-making by various stakeholders on low-risk health choices that may protect against dementia.

Register all longitudinal observational studies

Randomized controlled trials have strict requirements to publicly register their study design and hypotheses in advance, eg. in www.clinicaltrials.gov. No similar requirement exists for observational studies. Therefore, when appraising the results of such studies, it is generally unclear how many hypotheses were generated and tested to generate a single result reported in a publication. RCTs are also expected to analyze data according to a detailed pre-specified plan; analytic choices are usually much more numerous for observational studies and prespecified plans are rare, raising uncertainty about statistical design and the risk of selective reporting[14]. The rationale for prospective registration of observational research was recently discussed in detail by Weiderpass and colleagues, including the importance for the International Committee of Medical Journal Editors to change their policy to require prospective registration of Oss published in their member journals[15].

Validate exploratory results with confirmatory study designs

To raise the credibility and utility of observational studies for public health decisions, initial hypotheses generated by exploratory studies should be validated on independent observational data-sets. Validation studies should be held to confirmatory study design standards, required to register pre-specified hypotheses for precisely defined exposures or interventions and outcomes, with detailed protocols or analysis plans in advance of analyzing the data, and justification of why the proposed sample-size provides adequate power to test the hypothesis [12].

Raise reporting standards to enable independent evaluation of bias in study design

Both RCTs and observational studies tend to generate exaggerated estimates of the effectiveness of exposure or interventions [16], usually as a result of biased measurement of outcomes, attrition, or selective reporting. However, the risk of these biases affecting RCTs may be reduced through specific design features (e.g. blinding of outcome measurement) and more easily detected because of formal reporting standards including the requirement for prespecified protocols[12] for study design and data analysis. The recent SPIRIT checklist of trial characteristics and features to be described in RCTs protocols seeks to improve their quality [17].

Most of the standards for RCTs set out in the CONSORT Statement [18] can and should be applied to confirmatory observational cohort studies designed to estimate the effects of an intervention. Other observational studies can follow the guidelines developed by STROBE (Strengthen The Reporting of Observational Studies in Epidemiology), a collaborative initiative with check-lists for reporting of cohort studies, case-control studies, and cross-sectional studies, as well as conference abstracts [19]. Reporting standards should clearly identify studies as exploratory or confirmatory. Although reporting standards will not raise the quality of the analyses per se, adherence to the standards allows users of the evidence to appraise the risk of bias and the quality of study design. Empowering users to appraise research is critical to maximize the usefulness of observational data for dementia prevention.

Invest in effectiveness research from observational studies

Randomized controlled trials for prevention have often been criticized for testing interventions for too short a duration or too late in a disease process to detect a benefit that may accumulate slowly over decades. Conversely, the rigor of trial designs (eg, a very specific dose of treatment, a very specific age group, a very specific level of patient health) yield directly relevant evidence on the effectiveness of that intervention at that stage of life/health. Such specificity can directly inform patients', doctors', and policy makers' decisions about future management for the kinds of people who took part – typically people are concerned about their cognitive health because they are older and already experiencing cognitive decline.

In contrast, the majority of observational studies have explored etiology and risk factor associations, i.e., the identification and quantification of the risk of a disease conferred by a broad 'exposure,' usually a lifestyle, health behavior, or circumstance of living. Such etiological research can suggest possible causes of the disease but it is not equivalent to rigorous evidence for the effectiveness of one specific, well-defined intervention (eg. 400IU of vitamin E daily for three years) to reduce exposure to the risk factor in one well-defined population [12]. For example, broad evidence that low intake of fish and omega-3 fatty acids is associated with a higher risk of dementia [20] is not evidence that public health interventions to encourage fish intake will reduce dementia incidence. That is, unless major assumptions are made, it is unclear what dose of fish intake may give rise to an important benefit, what types of fish may be most beneficial, the age (or stage of development of disease) when a person needs to increase fish intake, or the number of years that high fish intake must be maintained. Similarly, diabetes is often associated with a higher risk of dementia [2] but whether specific treatments to prevent diabetes or improve glycemic control in diabetes can also reduce the risk of dementia has been less studied, including the duration, time-frame, and treatment necessary to reduce dementia risk. Thus, again, observational studies have not provided directly actionable interventions.

Some questions about the benefits or harms of specific interventions may be addressed with longitudinal observational data by analyzing in detail how changes in a given lifestyle or treatment variable are associated with subsequent cognitive outcomes, such as adoption of a Mediterranean diet, daily walking for one-half hour per day, or participating in programs that assist in weight loss. However, the data from individual cohorts may often lack the

power needed to yield results which are sufficiently detailed to produce actionable public health recommendations. This limitation that may sometimes be addressed by pooling data from different cohorts or databases, as described below; that is, by combining data from multiple cohorts, very fine exposure categories could be created which may then produce results to directly inform health guidelines. Data-sets for new large cohorts may also be built using cost-effective internet and smart-phone based technologies to gather highly detailed longitudinal information. Expanded investment in effectiveness research from observational data could yield more practical information for low-risk actionable health choices and dementia prevention.

Foster data-pooling and data-sharing

Individual observational studies often examine cohorts that are too small to provide sufficient statistical power to assess the effectiveness of specific interventions with information on treatment type, magnitude, duration, and the time-frame of use within the disease trajectory. They also typically lack the power to deal with heterogeneity of disease or intervention efficacy, such as the interaction of a given intervention or risk factor with genotype, comorbidities, and nutrient combinations. Data-pooling can optimize the use of existing data to cost-effectively raise power to address more complex and subtle questions although data pooling *per se* does not reduce the risk of bias. On the other hand, data-pooling may resolve some concerns from publication bias by unearthing data that has been gathered from large cohorts but not published because of negative findings, lack of publication impact, or time restrictions.

Data-pooling can be facilitated when researchers share their data on centralized and sometimes open-access databases such as the National Archive of Computerized Data on Aging (http://www.icpsr.umich.edu/icpsrweb/NACDA/), Synapse (http://sagebase.org/synapse-overview/), Figshare (http://figshare.com/), Dryad Digital Repository (http://datadryad.org/), and the Neuroscience Information Framework (http://www.neuinfo.org/). The data from some cohorts cannot legally be contributed into open-access repositories because of restrictions in the consent forms signed by participants. However, some web-based interface platforms can allow individual researchers to maintain control of their data while facilitating analyses that pool data among collaborators. For example, the Global Alzheimer's Association Interactive Network (GAAIN; http://www.gaain.org/) has created a computational infrastructure along these lines.

For some recent cohorts, investigators have implemented innovative consent forms that enable data-sharing, such as Portable Legal Consent developed by Sage Bionetworks [21]. The Alzheimer's Disease Neuroimaging Initiative (http://www.adni-info.org/) and the Health and Retirement Study (http://hrsonline.isr.umich.edu/) are high-profile studies that share de-identified cohort data. Distinct types of observational data may be linked, such as electronic medical records and biobanks that have been linked in cost-effective alternatives to traditional patient cohorts for pharmacogenomics[22]. Further, data-sharing could be facilitated by cohort consortiums like the National Cancer Institute Cohort Consortium, the CHARGE consortium for genomic epidemiology of heart and aging research [23], and the Social Science Genetic Association Consortium [24].

While data-pooling and open-access data-sharing have substantial promise, they require resources, time, harmonization, and logistics. Clear standards for conduct, design, and reporting must be established to ensure quality and enable systematic reviewers to recognize when overlapping datasets have been used in distinct publications, so that specific data-sets do not exert a mistakenly large influence [25]. Some data sources are expensive and pooling data across studies often requires substantial data management and complex analyses, as well as detailed prespecified analysis plans. Researchers need funding from granting agencies for this kind of work and wider recognition by academic institutions of its value. Publication credit can help, such as efforts like Figshare and the *Scientific Data* journal launched in 2014 by Nature Publishing Group. The Bioresource Research Impact Factor can give credit to researchers who create valuable databases [26]. Overall, investment in data-pooling and data-sharing can pay off by expanding the utility of existing and future datasets.

Encourage standardized exposure and outcome measures

Combining different bodies of evidence to address any given research question is impaired by major differences in exposure and outcome measures. In cohort studies, the exposure variables for physical activity have been measured as categorical estimates of “low, middle or high” or “sedentary versus active” versus continuous variables of calories burned, distance traveled on foot, and time spent exercising [27]. Outcomes also vary widely: some studies assay clinical diagnosis of Alzheimer’s, some all-cause dementia, some a prescription for acetylcholinesterase inhibitors. Other studies avoid clinical diagnoses and rely on diverse assays of cognitive decline that may or may not relate to incident diagnosis of dementia.

In this context, it is challenging and sometimes impossible to determine whether results across studies are truly in agreement or not or simply too diverse to compare. Although some diversity of exposure measurements may raise the ability to detect the “active ingredient” of an association, the use of standard exposure and outcome measures could improve the ability the interpret a body of evidence for a specific therapeutic question. Valuable lessons may be learned from other fields that have tackled similar concerns, such as the pioneering research of OMERACT, Outcome Measures in Rheumatology (http://www.omeract.org/), which has in turn led to the wider COMET initiative for Core Outcome Measures in Effectiveness Trials (www.comet-initiative.org/).

Communicate the evidence and its strength to the public

No intervention has been proven unequivocally to decrease the risk of dementia, but when is the evidence sufficient for action by individuals, doctors, or public health authorities? The answer depends on the person who makes the decision. Even with extensive population-based evidence, an individual patient’s choice should depend on his or her specific situation, including overall health and illnesses, lifestyle, and preferences for potential benefits, risks, and costs. To ensure that the existing science can be used as effectively as possible for diverse decisions, the evidence and its quality should be communicated in a clear and credible manner whether or not it is sufficient for a public health recommendation.

The choice of statins for primary prevention of cardiovascular disease in low-risk individuals is an example of individual decision-making in the setting of extensive population-based evidence. In people with a low risk of cardiovascular disease, statins may [28] or may not [29] significantly reduce overall mortality depending on the statistical analysis and included data. Statins reduce the risk of myocardial infarction and stroke with a need to treat 140 low-risk patients to prevent one event, but may also raise the risk of diabetes by 10 to 50 percent and the risk of musculoskeletal disorders with 1 harm in every 37 to 47 patients treated [29]. Missing information, short trial duration, and other concerns suggest that the RCTs have not adequately characterized the risk-benefit profile for low-risk patients [29; 30; 31]. Clinicians are advised to assist low-to-moderate risk patients in making the benefit-harm decision on an individual basis [29; 31].

For questions of dementia prevention, the quality of the evidence is substantially lower than that for statins and cardiovascular protection. The evidence that does exist is typically communicated to the public in a piece-meal fashion through popular media of varying quality and by advocacy groups. The evidence from a single in vitro or animal study may be portrayed in the same way as evidence from a large carefully conducted meta-analysis of prospective cohort studies. Individuals who are searching for information about dementia prevention are left in a fog.

Most of the potential strategies for dementia prevention will affect health and well-being beyond the brain. This risk/benefit profile is important when evaluating whether the evidence is sufficient for a given action. For example, moderate actions to reduce social isolation may protect against dementia with relatively few risks and potential benefits to quality of life, depression risk, and general health [32]. On the other hand, observational evidence suggest that long-term use of ibuprofen might perhaps protect against dementia [33] but the rationale is weakened by other data that high-dose chronic ibuprofen raises the risk of hypertension[34], a risk factor for dementia, as well as major coronary events and gastrointestinal complications[35]. Even “low-risk” strategies such as increasing exercise require time and money that will impact quality of life and be weighed differently by individuals with distinct risks and priorities.

How can the existing evidence be made as useful as possible for the choices made by individuals? The initial need is to communicate the science behind a given action, the strength of the evidence, and the potential risks and benefits. However, few individuals will have the knowledge or skills to use and understand this information no matter how clearly it is described. Individuals often entrust their health decisions to doctors as knowledgeable interpreters of the evidence. Unfortunately, most doctors lack the time to adequately discuss the risks and benefits for all their patients’ health choices. They also lack the time and sometimes the training to read and interpret the most current scientific evidence.

Complementary strategies to communicate information to individual citizens and doctors should be encouraged. Internet-based decision-aids can provide evidence-based summaries and a framework for individuals and clinicians to integrate diverse variables and preferences into an evidence-based personalized decision. Internet-based decision-aids are already available to help patients decide whether to take treatments for menopausal symptoms

(Menopause Map from the Hormone Health Network) and osteoporosis after menopause (AHRQ). For several other diseases, evidence for risk factors developed primarily from observational studies has been translated into risk calculators to help individuals understand their risk of various diseases based on age, body-mass index, ethnicity, lifestyle, family history, and other factors, with customized recommendations to reduce disease risk (eg. www.yourdiseaserisk.wustl.edu). Similar tools may be useful for dementia risk. Other sites aim to explain the quality of the scientific evidence available for dementia prevention strategies (eg. cognitivevitality.org; alz.org/research/science/alzheimers_prevention_and_risk.asp).

Tools like these can help people understand their risk of dementia and the potential effect of modifiable risk factors. They can also enable people make decisions on the basis of incomplete evidence if they explain the quality of the evidence and the strength of a potential association or effect. The resources required are considerable, particularly given the need to update tools regularly based on emerging research. If done carefully, however, such tools could maximize the usefulness of scientific research for the general public, whether that research derives from preclinical studies, observational studies, or randomized trials.

Summary of Recommendations to optimize the use of observational studies for decision-making on dementia prevention

1. Register all longitudinal studies
2. Validate initial exploratory results regarding dementia prevention with confirmatory studies of independent observational datasets that use established methodological and reporting standards to ensure that results meet the highest possible standards of quality and transparency.
3. Raise reporting standards to improve the ability of independent experts applying evidence-based methods to evaluate the quality and risk of bias in non-randomized studies.
4. Invest in effectiveness research using observational design in order to improve the evidence-base for specific decisions related to dementia prevention.
5. Encourage and facilitate data-pooling and data-sharing when opportunities exist to maximize the utility of unpublished data and raise power for research on the effectiveness of dementia prevention strategies and the heterogeneity of dementia progression and risk.
6. Establish standardized outcome and exposure metrics to improve the capacity to interpret a body of evidence regarding a specific question on dementia prevention.
7. Communicate the evidence to the general public using accessible internet-based tools and decision-aids to facilitate better informed evidence-based personal decisions. These communications should clearly state the risk of bias of the research and the broad potential ramifications relevant to the public.

Conclusion

Scientific evidence suggests that choices today may reduce the number of dementia patients tomorrow. The evidence is not conclusive and comes primarily from observational studies. Over time, the evidence available from randomized trials will increase for many questions, particularly given the important efforts underway to improve the quality of the evidence through the design and funding of randomized trials and biomarker development. However, opportunities also exist to improve the quality and transparency of observational studies, and to communicate the available evidence to the public to facilitate informed decision-making. These opportunities are particularly important for dementia prevention strategies that are low-risk yet may require decades of use or multi-domain interventions in order to reduce the risk of dementia.

In 1965, Sir Austin Bradford Hill laid out nine criteria necessary to prove causality: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. Only one of these criteria requires randomization.

Acknowledgments

Funding: The authors of this paper participated in an advisory panel convened by the Alzheimer's Drug Discovery Foundation (ADDF) in April 2013 on *Alzheimer's Disease Prevention: improving the translation of diverse and incomplete scientific evidence into clinical and public health recommendations.* The panel and manuscript were funded by the ADDF. The cost of authors' time spent on this project was funded by NIH P30AG10161 for DAB, NIH K24AG031155 for KY, and NIH P50 AG005134 and Fidelity Biosciences for DB.

We thank Molly V. Wagster, PhD from the National Institute on Aging for contributing to the panel and providing feedback on the manuscript. We thank James McNally, PhD, National Archive of Computerized Data on Aging, University of Michigan, Ann Arbor, MI, for participating in the panel. We thank Ivan Oelrich, PhD, for astute editing.

References

1. Prince, M.; Prina, M.; Guerchet, M., et al. World Alzheimer Report 2013. London Alzheimer's Disease International (ADI); 2013. Journey of Caring: an analysis of long-term care for dementia.
2. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 2011; 10:819–828. [PubMed: 21775213]
3. Lin PJ, Yang Z, Fillit HM, et al. Unintended benefits: the potential economic impact of addressing risk factors to prevent Alzheimer's disease. Health affairs. 2014; 33:547–554. [PubMed: 24711313]
4. Kaplan BJ, Giesbrecht G, Shannon S, et al. Evaluating treatments in health care: the instability of a one-legged stool. BMCMedResMethodol. 2011; 11:65.
5. Carrillo MC, Brashear HR, Logovinsky V, et al. Can we prevent Alzheimer's disease? Secondary "prevention" trials in Alzheimer's disease. AlzheimersDement. 2013; 9:123–131.
6. Yaffe K, Tocco M, Petersen RC, et al. The epidemiology of Alzheimer's disease: laying the foundation for drug design, conduct, and analysis of clinical trials. AlzheimersDement. 2012; 8:237–242.
7. Richard E, Andrieu S, Solomon A, et al. Methodological challenges in designing dementia prevention trials - the European Dementia Prevention Initiative (EDPI). JNeurolSci. 2012; 322:64–70.
8. Vellas B, Andrieu S, Sampaio C, et al. Endpoints for trials in Alzheimer's disease: a European task force consensus. Lancet Neurol. 2008; 7:436–450. [PubMed: 18420157]
9. Carrillo MC, Bain LJ, Frisoni GB, et al. Worldwide Alzheimer's disease neuroimaging initiative. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2012; 8:337–342.

10. Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: what it is and what it isn't. Bmj. 1996; 312:71–72. [PubMed: 8555924]
11. Guyatt GH, Oxman AD, Kunz R, et al. What is “quality of evidence” and why is it important to clinicians? Bmj. 2008; 336:995–998. [PubMed: 18456631]
12. Reeves BC, Higgins JPT, Ramsay C, et al. An introduction to methodological issues when including non-randomised studies in systematic reviews on the effects of interventions. Research Synthesis Methods. 2013; 4:1–11. [PubMed: 26053535]
13. Norris, S.; Atkins, D.; Bruening, W., et al. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): 2008. Selecting Observational Studies for Comparing Medical Interventions.
14. Norris SL, Moher D, Reeves BC, et al. Issues relating to selective reporting when including non-randomized studies in systematic reviews on the effects of healthcare interventions. Research Synthesis Methods. 2013; 4:36–47. [PubMed: 26053538]
15. Dal-Re R, Ioannidis JP, Bracken MB, et al. Making prospective registration of observational research a reality. Science translational medicine. 2014; 6:224cm221.
16. Ioannidis JP. Why most published research findings are false. PLoSMed. 2005; 2:e124.
17. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Annals of internal medicine. 2013; 158:200–207. [PubMed: 23295957]
18. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. International journal of surgery. 2011; 9:672–677. [PubMed: 22019563]
19. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Journal of clinical epidemiology. 2008; 61:344–349. [PubMed: 18313558]
20. Cunnane SC, Chouinard-Watkins R, Castellano CA, et al. Docosahexaenoic acid homeostasis, brain aging and Alzheimer's disease: Can we reconcile the evidence? Prostaglandins LeukotEssentFatty Acids. 2012
21. Vayena E, Mastroianni A, Kahn J. Caught in the web: informed consent for online health research. Science translational medicine. 2013; 5:173fs176.
22. Bowton E, JRF, Wang S, et al. Biobanks and Electronic Medical Records: Enabling Cost-Effective Research. Science translational medicine. 2014; 6
23. Psaty BM, O'Donnell CJ, Gudnason V, et al. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: Design of prospective meta-analyses of genome-wide association studies from 5 cohorts. Circulation Cardiovascular genetics. 2009; 2:73–80. [PubMed: 20031568]
24. Rietveld CA, Medland SE, Derringer J, et al. GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. Science. 2013; 340:1467–1471. [PubMed: 23722424]
25. Khachaturian AS, Meranus DH, Kukull WA, et al. Big data, aging, and dementia: Pathways for international harmonization on data sharing. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2013; 9:S61–62.
26. Cambon-Thomsen A, Thorisson GA, Mabile L, et al. The role of a bioresource research impact factor as an incentive to share human bioresources. Nature genetics. 2011; 43:503–504. [PubMed: 21614086]
27. Harrington, M.; Weuve, J.; Blacker, D. [accessed Oct 21, 2013] Physical Activity. The AlzRisk Database. 2012. http://www.alzrisk.org
28. Mihaylova B, Emberson J, et al. Cholesterol Treatment Trialists C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012; 380:581–590. [PubMed: 22607822]
29. Abramson JD, Rosenberg HG, Jewell N, et al. Should people at low risk of cardiovascular disease take a statin? Bmj. 2013; 347:f6123. [PubMed: 24149819]
30. Munoz D, Granger CB. ACP Journal Club. Review: Statins reduce mortality and cardiovascular (CV) morbidity in patients with low CV risk. Annals of internal medicine. 2012; 156:JC4-07. [PubMed: 22508747]

31. Seehusen DA. Statins for primary cardiovascular prevention. American family physician. 2011; 84:767–768. [PubMed: 22010612]

32. Coley N, Andrieu S, Gardette V, et al. Dementia prevention: methodological explanations for inconsistent results. Epidemiologic reviews. 2008; 30:35–66. [PubMed: 18779228]

33. Vlad SC, Miller DR, Kowall NW, et al. Protective effects of NSAIDs on the development of Alzheimer disease. Neurology. 2008; 70:1672–1677. [PubMed: 18458226]

34. Morrison A, Ramey DR, van AJ, et al. Systematic review of trials of the effect of continued use of oral non-selective NSAIDs on blood pressure and hypertension. CurrMedResOpin. 2007; 23:2395–2404.

35. Bhala N, et al. Coxib traditional NTC. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013; 382:769–779. [PubMed: 23726390]