

**Weaving threads of evidence into knowledge: The need for
contextualized developmental theories of risk factors for age-related
disease**

Paper prepared for the Academy of Social Sciences in Australia Workshop
“Theoretical, Empirical and Policy Inputs to Modelling Healthy Ageing”
December 5-6, 2007

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The emergent ethos of ‘open access’ is breaking down barriers to data-sharing in social science whilst we are simultaneously moving into an era in which technology will allow for the analysis of much larger datasets. There is increasing information available from longitudinal studies on associations between putative risk factors and outcomes such as diabetes, dementia, depression, stroke, obesity, and longevity. The volume of available information and data provides unprecedented opportunities for understanding how factors contribute to disease. However, new frameworks, theories, and methodological expertise are required to develop and test statistical models that accurately represent and make sense of human development and disease.

This paper explores the interpretational and methodological issues involved in the identification of risk factors for diseases of late-life. Specific examples are drawn from research on risk factors in the field of lifespan cognitive development and dementia epidemiology, including alcohol consumption, smoking and serum cholesterol. These factors are all modifiable, and are frequently mentioned in public health messages in relation to a range of diseases occurring in late life. All three risk factors have been examined for interactions with the APOE genotype, which is associated with Alzheimer’s disease (AD). However, the process of unraveling how these risk factors relate to dementia and cognitive decline reveals that they do not have straightforward direct causal relationships.

Example 1: *The history of science in relation to smoking and dementia*

Research in the 1990s suggested that smoking may be protective against dementia and that nicotine may be cognitively enhancing. Nicotine is a cholinergic agonist, and experimental studies have shown that administration of nicotine

improves short term cognitive performance in laboratory settings conducted by psychologists in both humans and rats¹. Laboratory studies show that nicotine inhibits amyloid formation² so there is a theoretical rationale underlying the scientific wisdom that smoking may be protective for dementia. However, as knowledge of the detrimental effects of smoking increased, such as the association of smoking with increased inflammatory markers implicated in a range of diseases³, views on smoking and dementia risk began to change. By 2000, authors argued that there was in fact no evidence that smoking is protective against dementia and that the known negative effect of smoking on cardiovascular disease meant that it was likely to be a risk factor for Vascular Dementia (VaD)⁴. However, in 2002, a systematic review of 21 case-control and 8 cohort studies examining smoking as a risk factor for AD found conflicting results⁵ regarding the direction of the association. This review found that case-control studies indicated that smoking is protective, but that cohort studies showed the opposite effect. By late 2005, enough prospective cohort studies had published their results to allow for a quantitative meta-analysis of the association between smoking and cognitive decline and smoking and dementia sub-types. A systematic review published in 2007 showed that current smoking increases the risk of AD and VaD by 80%, and increases the rate of decline in Mini-Mental State Examination Scores⁶. It therefore appears that the short term improvements from exposure to nicotine in laboratory studies are far outweighed by the long term changes caused by chronic exposure. Thus, the consensus on smoking has changed from it being possibly protective, to it being a risk factor, within approximately 15 years. This example indicates that the time scale used to examine the association between a risk factor and an outcome may result in different conclusions being drawn about its effects.

Example 2: Alcohol and cognition: age of observation influences interpretation

A number of recent articles have shown that older adults who drink alcohol at light to moderate levels, have better cognitive performance⁷. Several studies have shown that such drinkers even have reduced rates of cognitive decline in late adulthood and a reduced risk of dementia⁸. The reasons suggested for the benefits of alcohol for cognitive performance have drawn from research on alcohol and cardiovascular disease⁹. However, research conducted on younger adults has also found that light to moderate drinkers have better cognitive function than abstainers¹⁰. The interpretation of this result in relation to young adults has received a different emphasis. The focus here has been on why abstainers perform worse on cognitive tests than drinkers, because in young adults it is extremely unlikely that participants have been exposed to alcohol long enough for long term effects to be evident. Moreover, cognitive abilities are still developing in young adults.

When viewed over the adult lifespan, the results suggest that at all ages, alcohol abstainers have lower cognitive test scores. This means that it is possible that alcohol itself may have no effect on cognition, and that all we are seeing in late life is the selection effects that were already evident in early adulthood! Without examining the association between alcohol consumption and cognition over the entire adult lifespan, it is not possible to determine whether alcohol influences cognitive decline in late life. This example illustrates the importance of examining health behaviours and cognitive outcomes over the entire adult life course. This is the only way to distinguish individual differences associated with choice of behavior, from the individual differences that are caused by specific behaviour.

Example 3: *Cholesterol and cognitive decline: An example of the need for complex models and complex questions*

With the growing recognition that cardiovascular risk factors also predispose individuals to dementia, there have been a number of studies evaluating the association between total serum cholesterol (TC) and late-life dementia. An implicit assumption in several recent articles is that high cholesterol, being a cardiovascular risk factor, would be particularly relevant to VaD, as opposed to AD. However, it is difficult to find evidence in the literature that reports results for cholesterol in relation to sub-types of dementia in support of this view. Recent evidence in fact suggests that high levels of serum cholesterol in mid-life are a risk factor for AD, rather than for VaD¹³.

Methodological issues relating to study design are particularly pertinent when TC is examined. Levels of cholesterol between cohorts and cultures with different diets, and inclusion of subjects with co-morbid conditions that lower cholesterol, may lead to inconsistencies in results¹⁴. It appears that the association between TC and cognitive decline may have a non-linear association with age, with authors suggesting that high TC in mid-life and low TC in late-life are associated with dementia and cognitive decline¹⁵. This means that observations based on cross-sectional studies may be confounded by age differences within samples¹⁶, and that prospective studies examining within-person change are optimal for uncovering the true nature of the association between TC and cognition and dementia. Where measurements are averaged across occasions of measurement in longitudinal studies, important information may be lost. Lack of consideration of these complexities may prevent the detection of significant interactions between risk factors such as high cholesterol, and APOE genotype.

General principles for studying 'risk' and risk factors

Some general principles about the study of risk factors can be extracted from the examples reviewed. These include the need to consider and model time-frames when examining risk; to consider short term variability and influences on performance versus long term change to the organization and structure of the organism¹⁷; to have statistical models of change, rather than averaging across time points, or creating difference scores; to separate domains of research and not necessarily infer that findings from one domain relate to another (animal versus human, experimental versus epidemiological, brain versus cognition) and the need to incorporate models of risk, and risk factor interactions, within social and historical contexts.

A further perspective that needs to be considered in modeling ageing and risk factors for age-related disease from a life-span perspective is that of the general public. Research suggests that widely held belief systems about risk factors for dementia do not necessarily reflect scientific evidence¹¹. Social scientists therefore need to be aware of the entire process of creating scientific knowledge about risk and behavior and how this translates into 'common knowledge' that will promote ageing well.

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Emerging Ageing Research Landscapes

- Availability of large cohort studies
- Open access
- Data pooling
- International comparison
- Increased capacity of software and hardware enabling higher level computation and modelling
- Greater collaboration
- Integration of social science and bioscience



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Challenges

- Developing cross-disciplinary expertise to meaningfully link types of knowledge
- Developing theories to encompass the available data
- Developing statistical methods that allow for testing of complex models
- Testing theories against data
- Creating facts and communicating knowledge
- Influencing policy

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Developmental Theory Distinguishes Becoming and Being

- Short term fluctuations in behavior are distinct from long term re-organization or change (cf. Ford, 1987, Li et al., 2004)
- Short term fluctuations seen as states (eg. Heart rate, emotion regulation, cognitive performance)
- Psychologists mostly study 'being'
- Long-term change results from chronic exposure leading to structural re-organization
- Influences on current states may have different influence on development

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Lifespan development approach

- Human development can only be understood by considering the entire life course
- Lifespan development occurs in social, historical, cultural context
- Brain development interacts with culture (cf. Baltes & Reuter Lorenz, 2006) 2-way
- Longitudinal research required to study development
- Information may need to come from different sources to piece together larger picture of development over the entire lifecourse – conception to death

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Cholesterol is a constituent of membranes and the source of steroid hormones.

Consumption as 'risk'

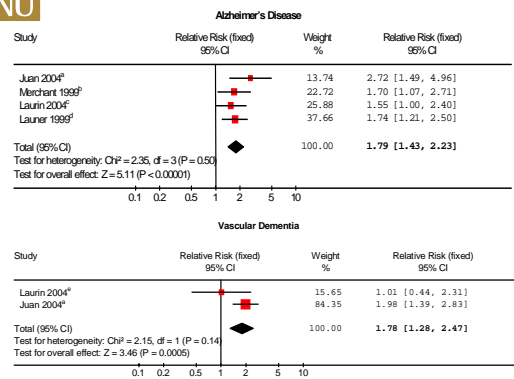
- Consumption is culturally, ethnically and individually determined
- Short term effects on function
- Influences the self-organization and structuring of the organism
- Long term effects on development and brain ageing

Smoking, drinking and eating!

- Modifiable through lifestyle, medication, social norms, culture
- Shared risk factors for multiple diseases and chronic conditions in late life
- 3 examples to illustrate methodological complexity and need for complex theories and models
- Issue of how science data leads to 'common knowledge'

1. Smoking, cognitive decline, dementia

- Laboratory evidence that nicotine improves memory performance in humans and rats
- Nicotine also inhibits amyloid formation
- Lerner et al., Lancet (1997) evidence of smoking & HRT being protective against dementia
- Review 2002 of case control studies found smoking protective, but cohort studies show opposite effect
- Opponents wrote editorials and letters but no definitive answer
- Systematic review 2007 demonstrative smoking risk



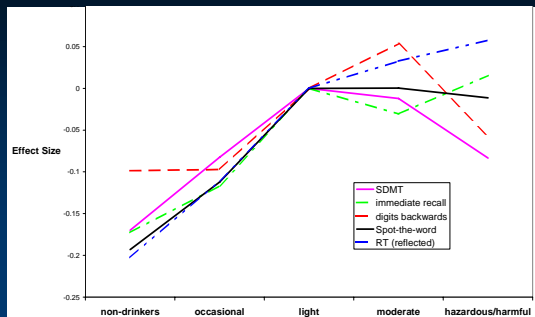
Lessons from example of Smoking

- Short term effects different from long term changes caused by consumption of a substance
- Levels of analysis don't necessarily transate (eg. Nicotine inhibits amyloid formation in the lab or improves rats running in a maze)
- Scientific facts are created
- Large amount of data collected over long periods of time are required to conclusively answer basic questions such as whether smoking is bad for your brain!

2. Alcohol, cognitive decline and dementia

- Deng et al. (2006) Light-Moderate Beer drinkers increased risk of dementia but light-Moderate wine drinkers reduced risk
- Excessive drinking > 14 p/wk female, > 21 p/wk males had 45% increased risk of dementia
- Mukamal 2003 (JAMA) found 1- 7 drinks per week associated with reduced dementia risk, interaction with APOE for heavy drinkers.
- Results support an inverse U with light drinking protectiveBUT **look at lifespan data**

ANU Cognitive performance and Alcohol PATH Consumption – no age differences



ANU Lessons from Alcohol and Cognition

- Selection effects health behaviour and consumption over the lifespan
- Lifespan data on relationship between risk factor and outcome is required to fully interpret level of risk
- Still unclear whether abstinence from alcohol is a risk factor, light alcohol is protective or whether abstainers are a different population to drinkers.

ANU 3. Cholesterol and dementia

- Assumption that high cholesterol would be a risk factor for vascular dementia in particular, and also AD
- General view that high cholesterol bad at any age

What does the evidence say?

1. High mid-life TC seems to be a risk factor for AD and any dementia
2. No evidence of TC being a risk factor for Vascular dementia
3. Systematic review found few significant associations and none for high late-life TC

ANU Studies on Cholesterol and AD

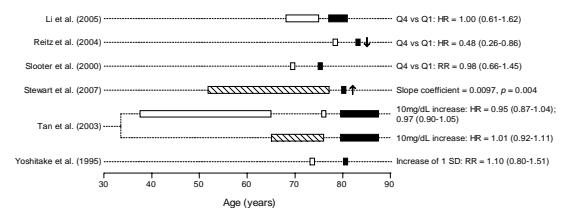


Figure. Bars and markers indicate the mean age at which, or mean age period over which, TC (□), change in TC (▨), and AD (■) were assessed. Arrows denote statistically significant relationships between either greater TC or greater decline in TC and the risk of AD (↑ increased; ↓ decreased).

ANU Lessons from Cholesterol

- Cholesterol has non-linear relationship with age
- Cholesterol has different relationships with different dementia sub-types
- Cholesterol possibly has non-linear relationship with dementia risk
- Not enough data on HDL and LDL
- Statistical models must examine change in level of the risk factor in relation to outcome
- Interactions with APOE, culture, diet, comorbidities
- Complex statistical models of cohorts followed for long periods of time are required

ANU General Principles for Examining Risk Factors

- Consider short-term effects vs long term changes caused by the risk factor
- Time frame of study is critical to interpretation
- Statistical models of change rather than averaging
- Findings don't necessary transfer across domains (laboratory to real world)
- Cultural context of consumption required to interpret results (eg. Alcohol = socio-economic factors)
- History of science - 'facts' are created and recreated



Public Knowledge and Common Knowledge

- Dementia literacy study (Low & Anstey 2007) showed that the public rated 'drink more water' as important as 'stopping smoking' to reduce dementia risk
- Generic views on health behaviours not in line with scientific findings, maybe not disease specific
- General health beliefs about nutritional factors
- Social context of knowledge creation
- Long process from lab to everyday understanding
- Understanding social context critical for translation of research on risk factors



Acknowledgements

- NHMRC Senior Research Fellowship
- Co-authors Chwee von Sanden, Agus Salim, Richard O'Kearney, Lee-Fay Low, Darren Lipnicki, Bryan Rodgers, Helen Christensen, Tony Jorm, Tim Windsor
- PATH Through Life Study, participants, Path Interviewers, Patricia Jacomb, Karen Maxwell