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The protected survivor model: Using resistant successful cognitive aging to identify protection in the very old

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ABSTRACT

For some cardiovascular risk factors, association with risk for cognitive impairment observed in early old age is reduced, or paradoxically even reversed, as age of outcome increases. Successful cognitive aging is intact cognition in the oldest-old; we define resistant successful cognitive aging as successful cognitive aging despite high risk. The protected survivor model posits that a minority of the general population has a protective factor that mitigates the negative effect of a risk factor on successful cognitive aging for the unprotected majority. As age increases, differential failure rates increase the proportion of survivors with protection. Among the unprotected, the proportion with low risk increases, but among those with protection, high risk and low risk do not differ. Due to differential mortality, half the survivors are eventually protected – a majority among those with high risk, and a minority among those with low risk. According to the protective survivor model, an example of Simpson's paradox, the association of the risk factor with survival does not change within an individual, but the association in the surviving population changes as its age increases.

We created quantitative illustrations of a simplified protected survivor model applied to successful cognitive aging to explain how the usual association of a risk factor with cognitive decline is reversed in the very old. In the illustrations, probability of subsequent survival was higher for survivors with high risk (mostly protected) than low risk (mostly not protected), an example of Simpson's paradox. Resistance to disease despite the presence of risk factors is consistent with the presence of countervailing protection. Based on the protected survivor model, we hypothesize that studies seeking protective factors against cognitive decline will be more effective by limiting a successful cognitive aging sample to resistant successful cognitive aging – to contrast with a sample without successful cognitive aging.

Introduction

Although disease is usually investigated as an exception from non-diseased normality, a third, seldom-investigated status is resistance to disease. True resistance to disease – attributable to a protection – is difficult to distinguish from lucky absence of disease, but is more plausible in those who remain healthy despite high risk. For example, resistance to HIV infection despite high-risk behavior was used to identify subjects among whom the protective Δ32 mutation in the CCR5 gene [1] was discovered. This paper presents a model for resistance, the protected survivor model, and applies it to offer a hypothesis about finding protective factors against cognitive decline in the very old.

In addition to their implications for mortality, many risk factors for cardiovascular disease (CVRFs) are risk factors against intact cognition [2], mostly for cognitive outcomes in early old age (average age through 75). For later old age outcomes, such associations are few and there are even some reversals – CVRFs associated with better outcome. However, the associations of CVRFs with both mortality and cognitive outcomes are also stronger for studies with earlier ages of risk assessment [3,4], for which the age at outcome is also typically earlier. In the statistical analysis section, Table 1 presents longitudinal studies of cognitive risk in normal subjects, predicted by total cholesterol or C-reactive protein (CRP) – two examples of CVRFs.

What can explain a reversed association within a study at very high outcome ages? A possible explanation is that the causal effect on cognition of the CVRF could similarly reverse within an individual with increasing age. In an antithetical explanation, the effect of the CVRF within an individual does not reverse with age – or may even accelerate. We previously offered a qualitative explanation of paradoxical reversals of the usual association of bad outcome with high risk [5]. In very old probands who maintained intact cognition, we found those with higher CRP levels had better concurrent memory [6], and had

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Table 1
Longitudinal studies associating higher total cholesterol and risk of bad cognitive outcomes.

Study	Nationality of sample	N in study	Mean age of risk factor measurement	Age of outcome assessment	Significant associations of CVRFs with bad cognition	Non-significant associations of CVRFs with bad cognition	Significant reversed associations of CVRFs with bad cognition
				Cholesterol			
Solomon et al., 2009 [12][a]	USA	9844	42	69	Alzheimer's disease (AD)		
Kivipelto et al., 2001a,b [13,14][b]	Finland	1449	50	71	Mild cognitive impairment (MCI), AD		
Yaffe et al., 2002 [15]	USA	1037	67	71	Cognitive impairment		
Toro et al., 2014 [16]	Germany	222	60	74	MCI, AD		
Reynolds et al., 2010 [17]	Sweden	815	64	74 [c]		Cognitive decline	
Whitmer et al., 2005 [18][a]	USA	8845	42	76	Dementia		
Solfrizzi et al., 2004 [19]	Italy	1445	73	76		MCI	
Notkola et al., 1998 [20][b]	Finland	444	47–66[b]	70–89[d]	AD		
Lorius et al., 2015 [21]	USA	223	76	78		MCI	
Mielke et al., 2010 [22]	Sweden	648	47[b]	79[b]		Dementia	
Taniguchi et al., 2014 [23]	Japan	682	76	79		Cognitive decline	
Yoshitake et al., 1995 [24]	Japan	826	74	81		AD	
Li et al., 2005 [25]	USA	2112	72	81		Dementia, AD	
Reitz et al., 2008 [26]	USA	854	76	81			MCI
Mielke et al., 2005 [27]	Sweden	382	70	81			Dementia
Tan et al., 2003 [28]	USA	1026	50[c]	83		AD	
				C Reactive Protein			
Marioni et al., 2010 [29]	Scotland (AAA)	2091	62	67	Cognitive decline		
Hoth et al., 2008 [30]	USA	78	71	72	Cognitive decline		
Marioni et al., 2010 [29]	Scotland (EAS)	534	63	74		Cognitive decline	
Yaffe et al., 2003 [31]	USA	2912	74	76	Cognitive decline		
Wichmann et al., 2014 [32]	USA	1947	67	77		Cognitive decline	
Ravaglia et al., 2007 [33]	Italy	804	74	78		AD	
Eriksson et al., 2011 [34]	Sweden	543	74	78		Dementia, AD	
Englehart et al., 2004 [35]	Netherlands	727	72	80		Dementia, AD	
Schmidt et al., 2002 [36]	USA	1050	55	80	Dementia, AD		
Lima et al., 2014 [37]	UK	266	77	81			Cognitive decline
Alley et al., 2008 [38]	USA	533	74	81		Cognitive decline	
Sundelof et al., 2009 [39]	Sweden	1062	71	82		Dementia, AD	
Laurin et al., 2009 [40]	USA	581	56	83		Cognitive decline	
Sundelof et al., 2009 [39]	Sweden	749	78	83		Dementia, AD	
Jenny et al., 2012 [41]	USA	833	76	85		Cognitive decline	
Tan et al., 2007 [42]	USA	691	79	86		AD	
van Himbergen et al., 2012 [43]	USA	840	73	86			Dementia, AD

[a] Dichotomized cholesterol ≥240 mg/dl
[b] Dichotomized cholesterol > 251 mg/dl
[c] Median age
[d] Only age range reported