

The Healthy User Effect: *Ubiquitous and Uncontrollable*

S. R. Majumdar, MD MPH FRCPC FACP

**Professor of Medicine,
Endowed Chair in Patient Health Management,
Health Scholar of the Alberta Heritage Foundation,
Faculties of Medicine and Dentistry and Pharmacy and
Pharmaceutical Sciences and School of Public Health,
University of Alberta, Edmonton, AB, Canada**

Take Home Messages

- **Non-randomized studies reporting “unanticipated” benefits of treatment should be interpreted with great caution**
- **Confounding by the healthy-user effect is ubiquitous and often a better or alternate explanation for unanticipated benefits**
- **The healthy-user effect probably cannot be controlled without randomized trials (or very rich clinical data)**

Interchangeable Terms Capturing the Same Construct

- **Healthy user effect**
- **Healthy user bias**
- **Healthy adherer effect**
- **Compliance bias**
- **Healthy vaccinee effect**
- **?Frailty bias**
- **?(Physician) selection bias**
- **etc**

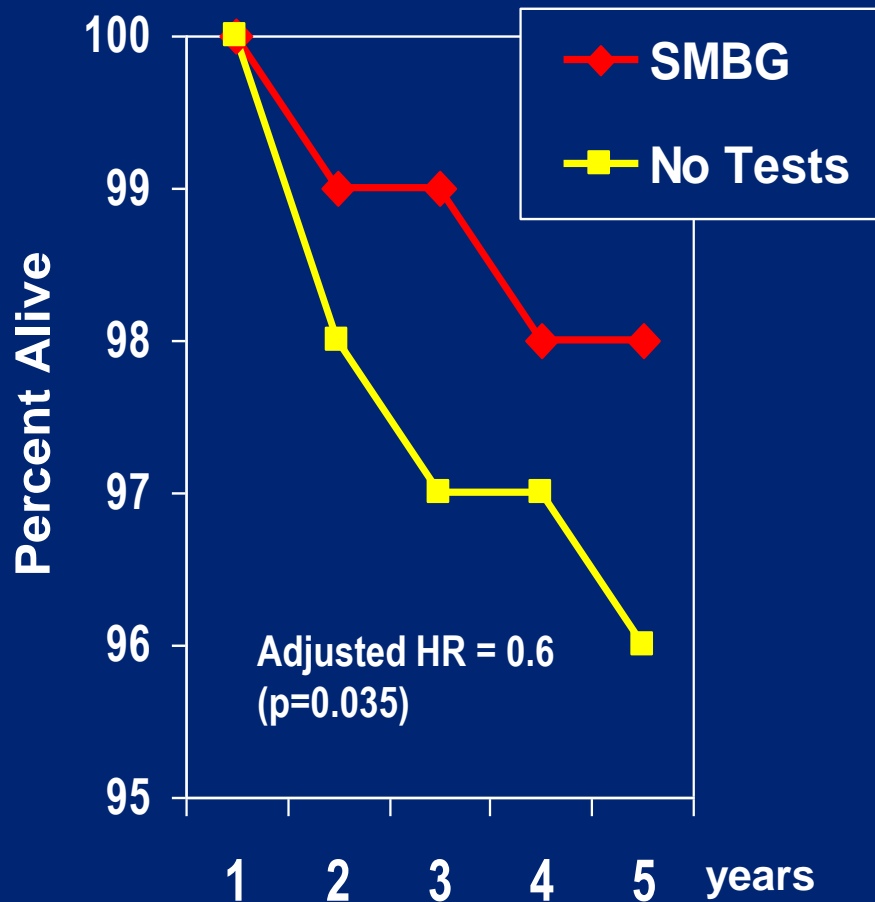
Statin “Effectiveness” in Two 70-Year Old Men 6-Months After ICD9-410x

- Doesn't take a statin
 - Doesn't fill any new Rx
 - Sort of takes old meds
 - Keeps smoking
 - Gains weight
 - Doesn't get labs done
 - Doesn't see family doc
 - Doesn't get flu jab
 - *Referred to me*
- Asks for and gets statin
 - Fills all new Rx
 - >80% pill adherence
 - Stop smoking
 - Loses weight
 - All labs done
 - Sees family doc q2m
 - Gets flu (and other) jabs
 - *Referred to cardiologist*

The Healthy-User Effect

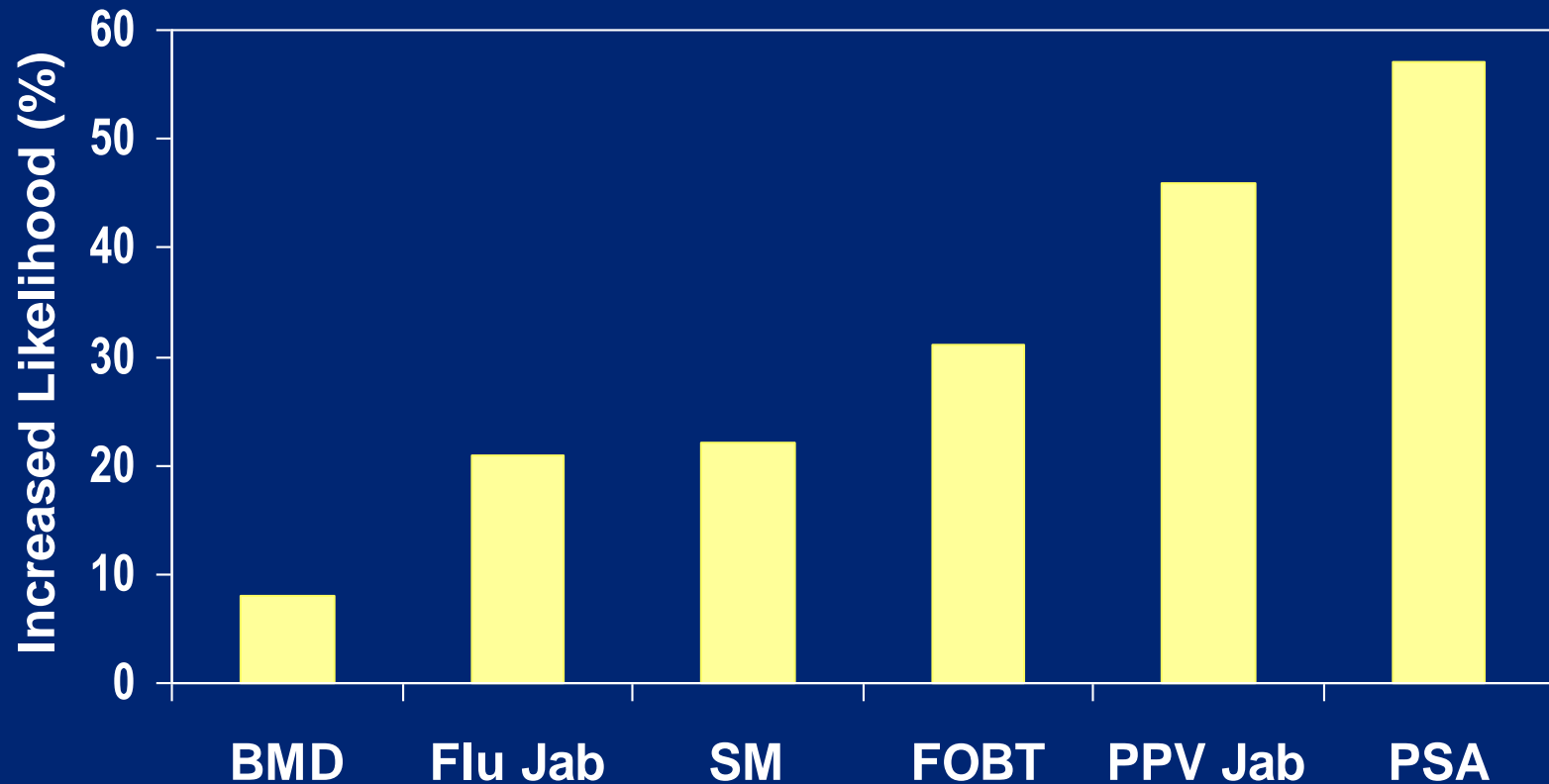
- The healthy-user tends to have:
 - less severe disease (for any given ICD-code)
 - higher socio-economic status
 - better functional, cognitive, health status
 - better habits re: diet, alcohol, smoking, exercise
 - greater inclination to screening (mammography, FOBT) and prevention (MD visits, immunization)
 - more motivation and health consciousness
 - **greater adherence to meds and other MD advice**

Good Adherence to Advice about Self Monitoring of Blood Glucose



- Incident cohort of 3268 patients with type 2 DM (ROSSO)
- SMBG defined as “1-year of testing”
- Extensive direct adjustment
- Result *independent* of glycemic control

Good Adherence to Meds Increases Likelihood of Good Adherence to Preventive Measures



(Brookhart et al. Am J Epi. 2007;166:348 and related “Preventive Services Index” recently developed by Williams et al. Prev Chronic Dz. 2010;7:110)

Good Adherence to Placebo

Coronary Drug Project Research Group 1980^{w1}

β blocker heart attack trial (men) 1990^{w2}

β blocker heart attack trial (women) 1993^{w3}

Canadian amiodarone myocardial infarction arrhythmia trial 1999^{w8}

Cardiac arrhythmia suppression trial 1996^{w4}

Physicians health study 1990^{w16}

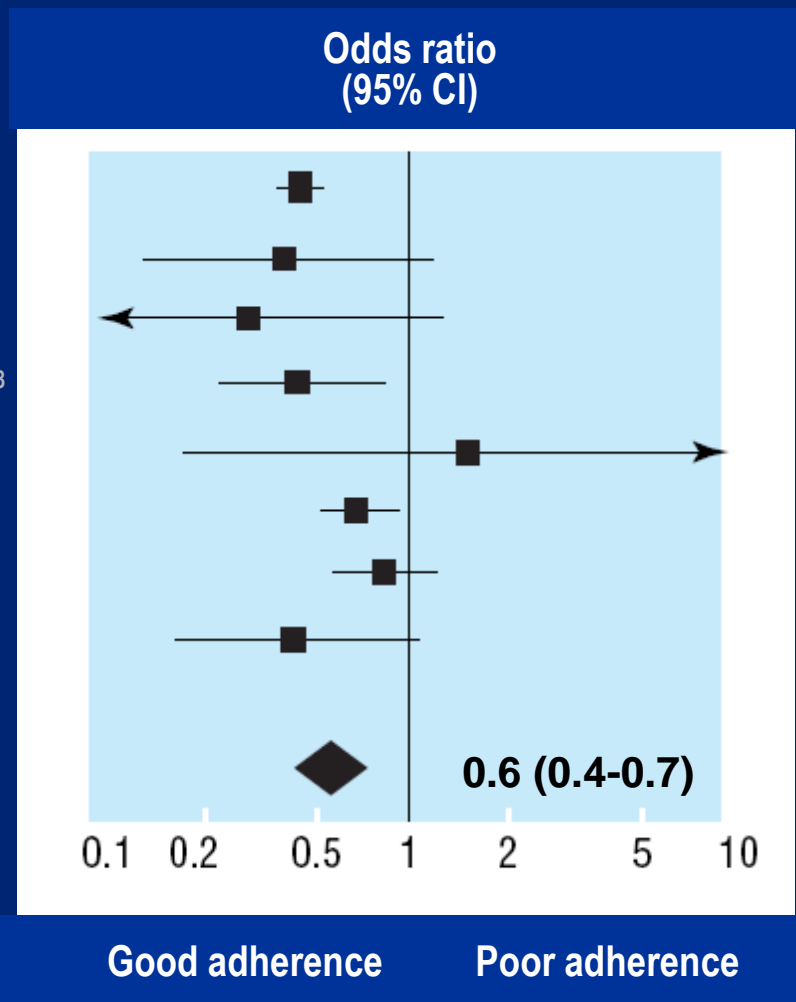
West of Scotland prevention study 1997^{w17}

University Group Diabetes Project 1970^{w22} 1971^{w18}

Total events: 581 (good adherence), 415 (poor adherence)

Test for heterogeneity: $\chi^2 = 14$ ($P = 0.05$) with $I^2 = 51\%$

Test for overall effect: $Z = 4$ ($P < 0.001$)



(Simpson SH et al. BMJ. 2006;333:15-9)

“Pleiotropic” Benefits of Good Adherence to Common Meds in Cohort Studies

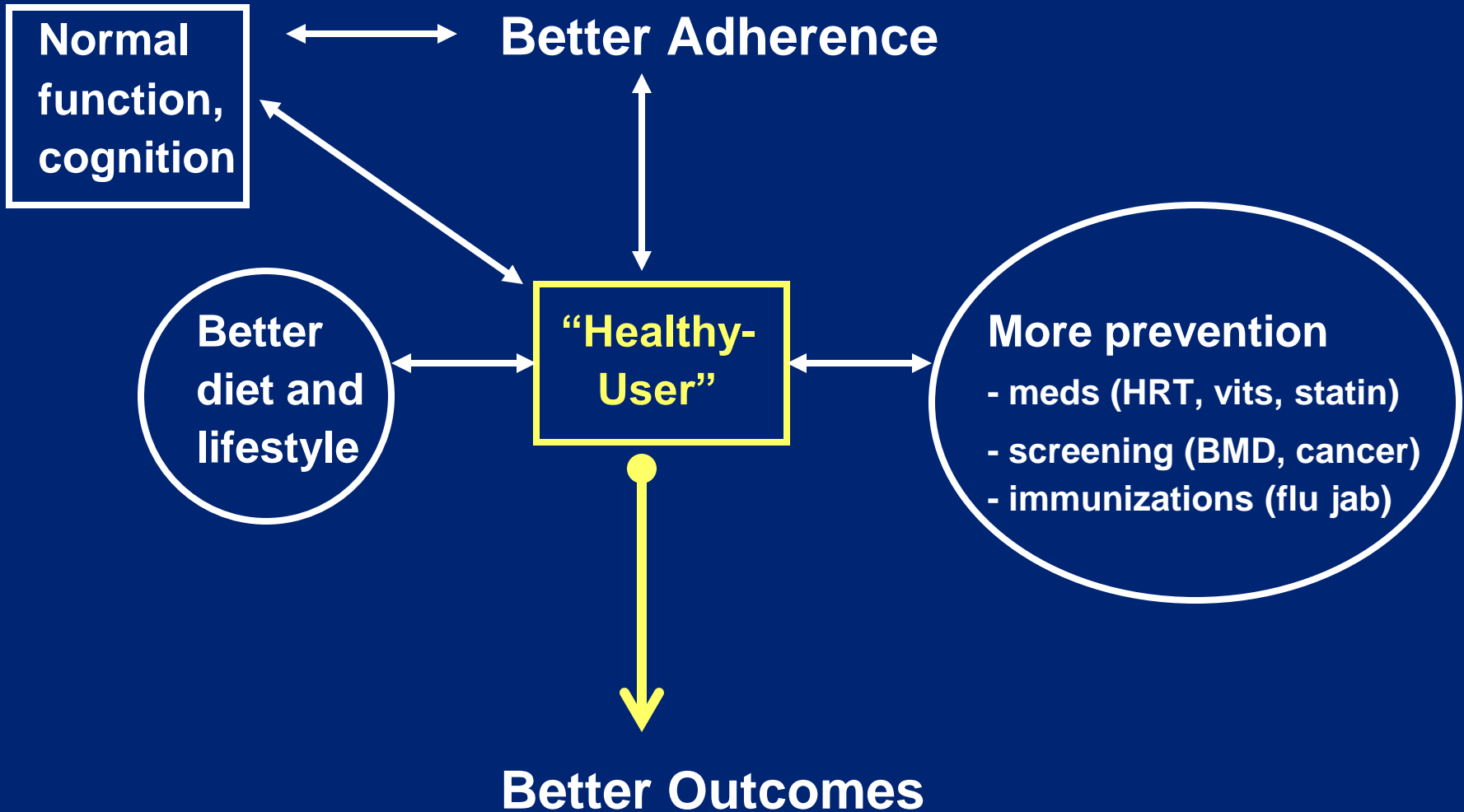
- **Post-menopausal hormone therapy**
 - Reduce hip fractures
 - Reduce gallstone-related disease
 - Prevent sepsis and infection-related death
 - Prevent dementia
 - Delay onset and progression of diabetes
 - Decrease colorectal cancer incidence

- **Statins**
 - Reduce hip fractures
 - Reduce gallstone-related disease
 - Prevent sepsis and infection-related death
 - Prevent dementia
 - Delay onset and progression of diabetes
 - Decrease colorectal cancer incidence

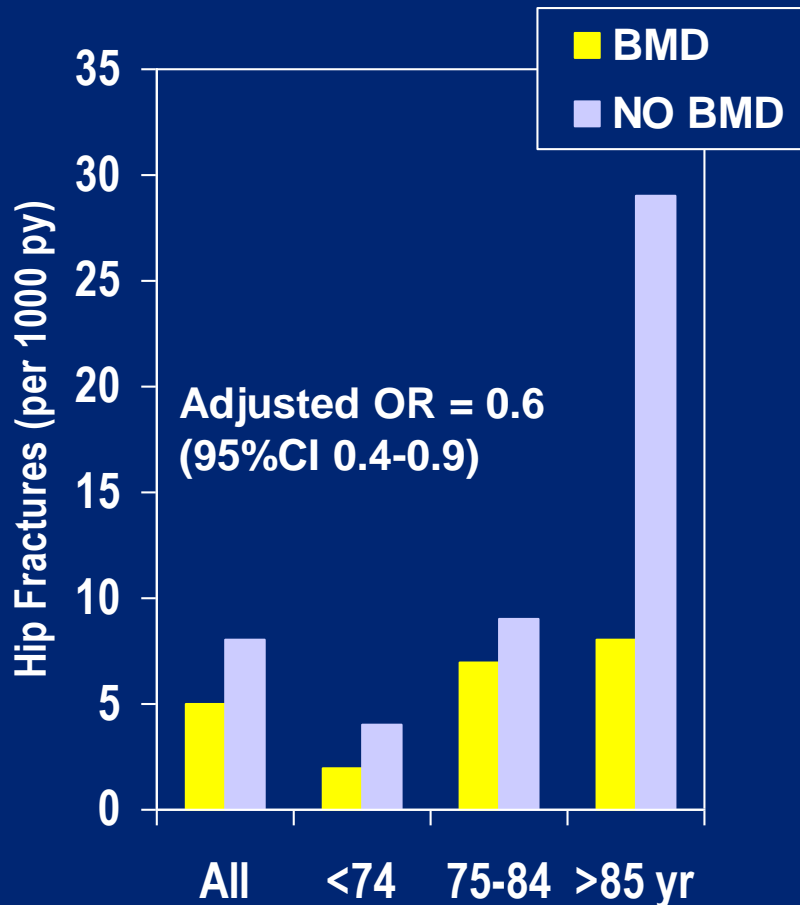
Good Adherence to Statins

<i>Outcomes of Interest</i>	Adjusted HR	95% CI	P-value
Intended Effects			
Myocardial infarction	0.72	0.67-0.78	<0.001
Emergency admission	0.87	0.85-0.89	<0.001
Implausible Associations			
Drug addiction	0.73	0.65-0.83	<0.001
Car accidents	0.75	0.72-0.79	<0.001
Poisoning	0.86	0.78-0.94	<0.001
Gout	0.89	0.85-0.89	<0.001

(Dormuth et al. Circulation. 2009;119:2051)



BMD Testing and Hip Fractures



- Elderly CHS cohort ~3100 with 6 yrs follow-up
- **BMD “offered” to some patients by investigators (~20% not offered)**
- Direct and PS adjustment using rich clinical data
- Results independent of starting osteo- meds

BMD Testing and Hip Fractures – *Differences in Rarely Captured Data*

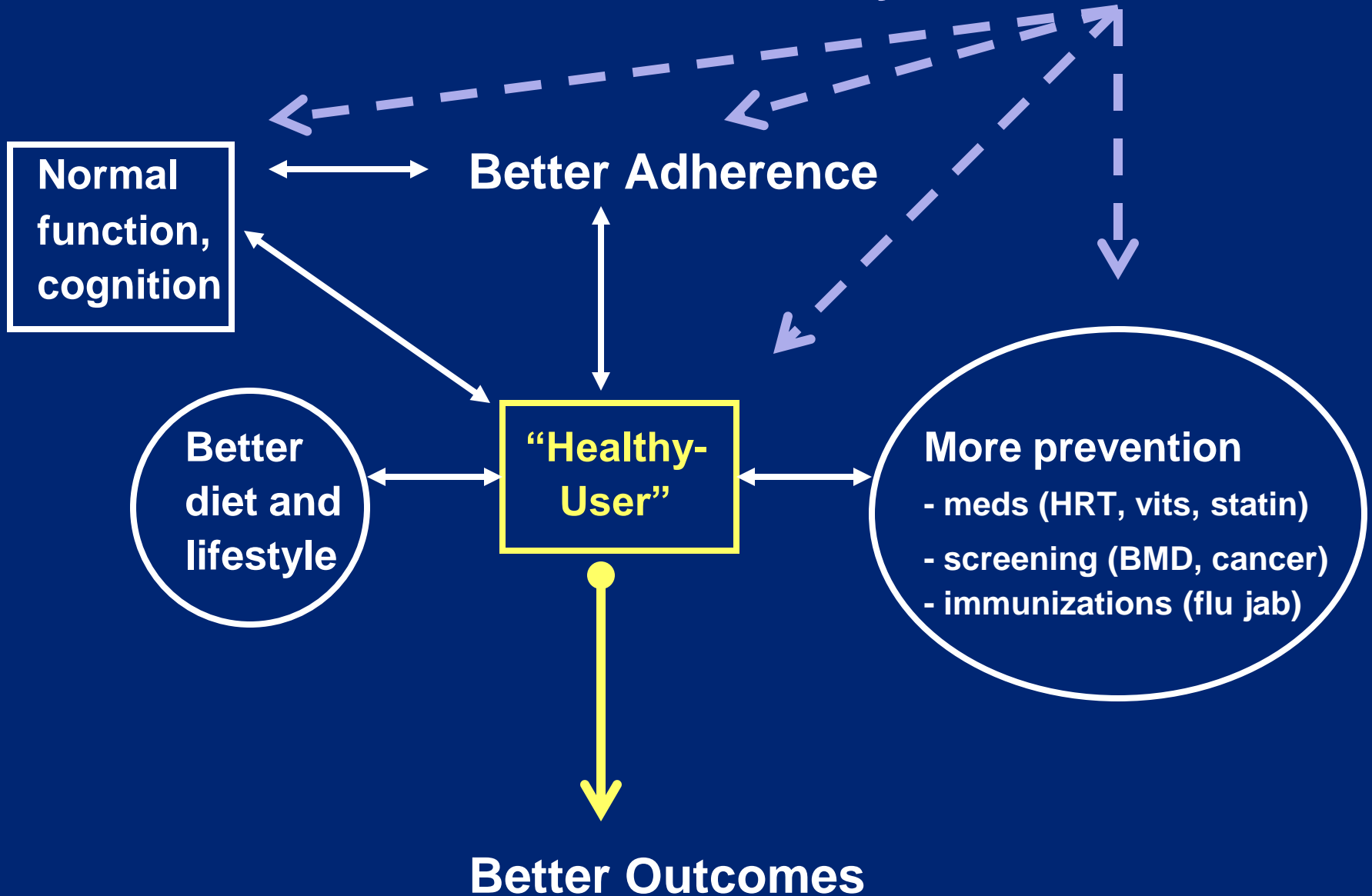
<i>Characteristics</i>	BMD test	NO test	P-value
College education	47%	29%	<0.001
Income > 25k per year	47%	40%	0.001
Good or better health status	44%	40%	0.02
Physical activity (kcal/wk)	820	716	0.001
Normal cognition	91%	86%	<0.001
Multivitamins	14%	8%	<0.001
Calcium supplements	9%	5%	<0.001

Effect of BMD Testing on Hip Fractures in ~ 70,000 Canadian Women over 10-years

<i>In the last 2-years...</i>	Adjusted HR Hip Fracture	95% CIs	P-value
Screening BMD	0.90	0.8-1.0	0.05
Screening Mammogram	0.88	0.77-0.99	0.04
Flu Jab	0.78	0.68-0.91	<0.001

(Majumdar et al, preliminary data, unpublished [2013])

Physician Selection Bias



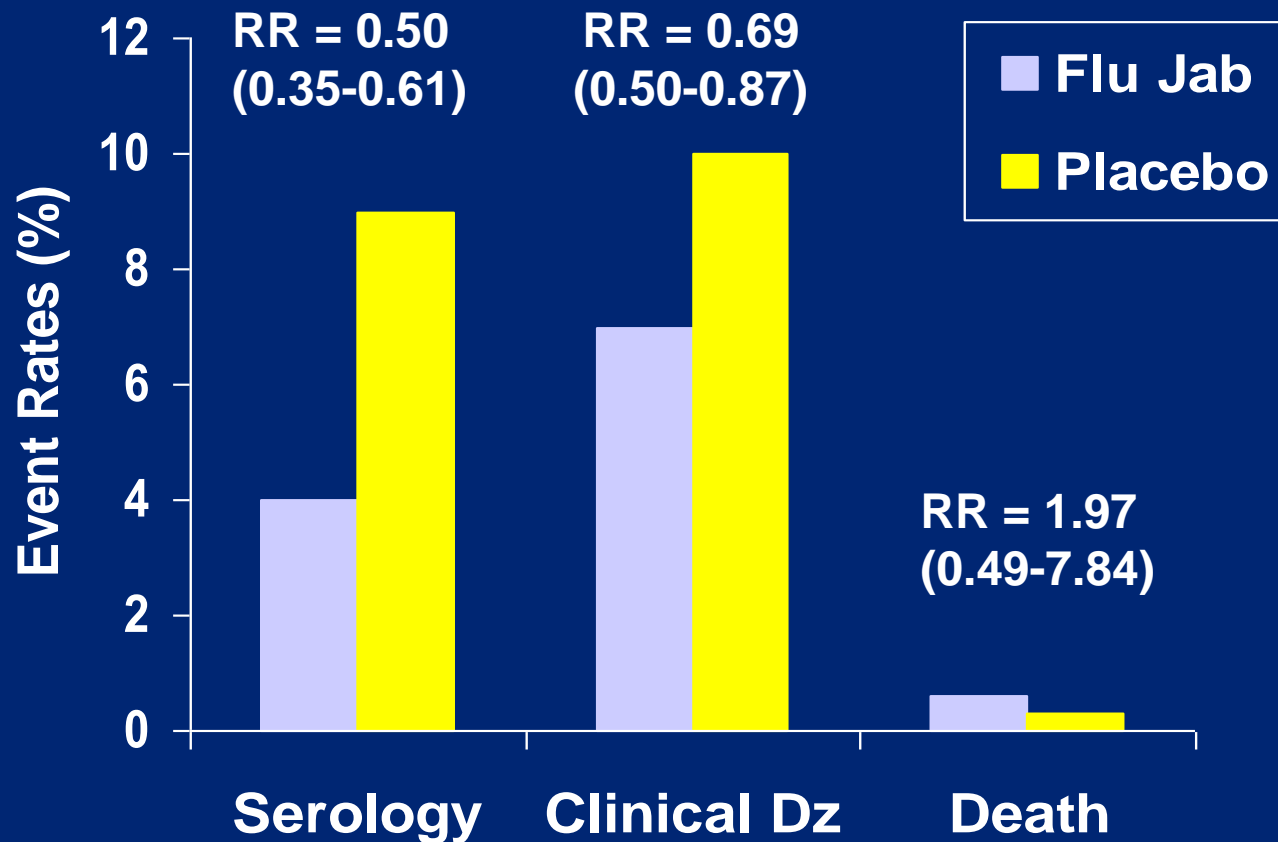
In summary (i)

- 1. Adherence central to the healthy-user effect**
- 2. Any measure of adherence captures many “unmeasured” health behaviors and patients destined to have better outcomes**
- 3. To the degree that physicians are good at selecting which patients are healthier and more likely to adhere to their advice the healthy-user effect might be at play**

Universal Flu Vaccine for the Elderly

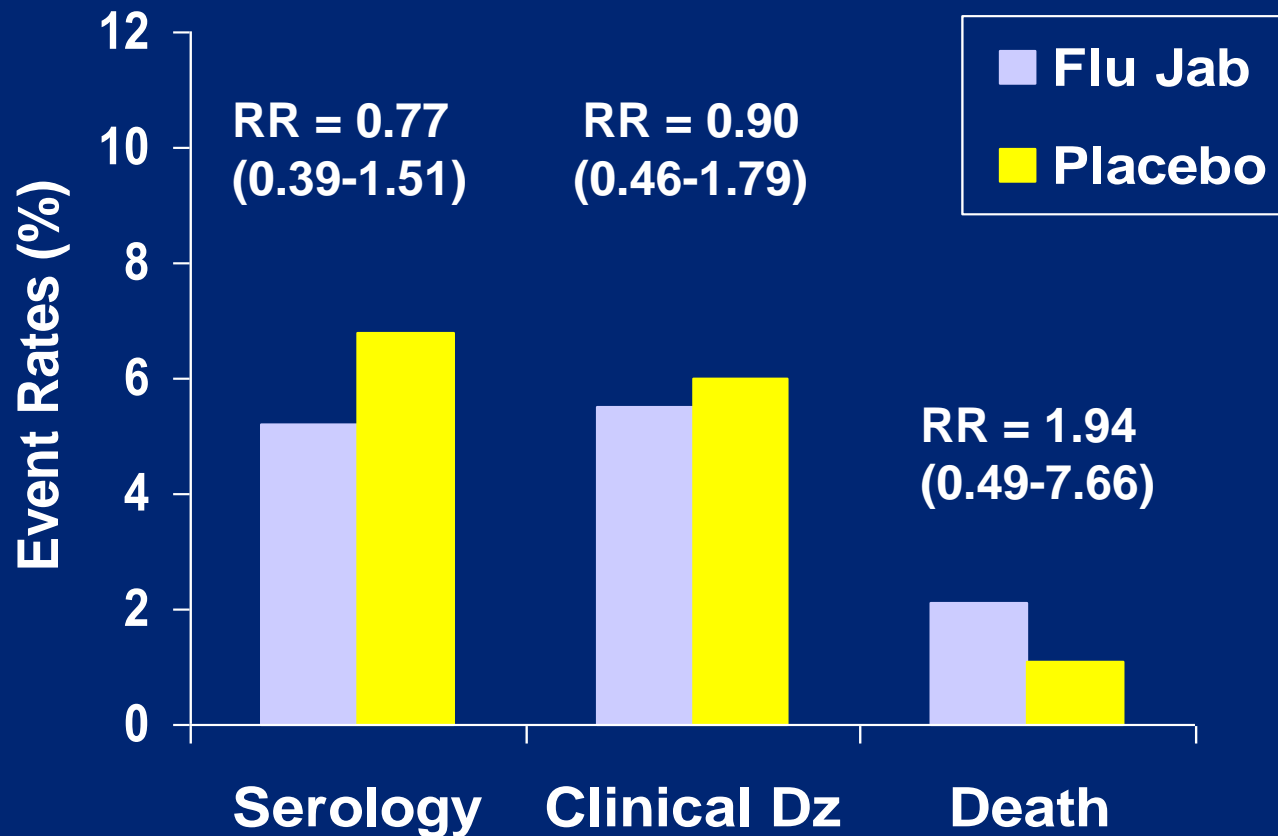
- Every year, massive flu vaccination efforts are undertaken in the fall and winter
- Efforts are not intended to prevent influenza transmission *per se*, rather intended to prevent winter-time hospitalizations and deaths
- Therefore, vaccination efforts directed at those at highest risk – the elderly (65-70 years and older)
- This leads to \$70 savings per person vaccinated and \$800 savings per life year gained each year

Meta-Analysis of All Randomized Trials of Flu Vaccine Effectiveness in Older Adults – One High Quality RCT (n=1838)



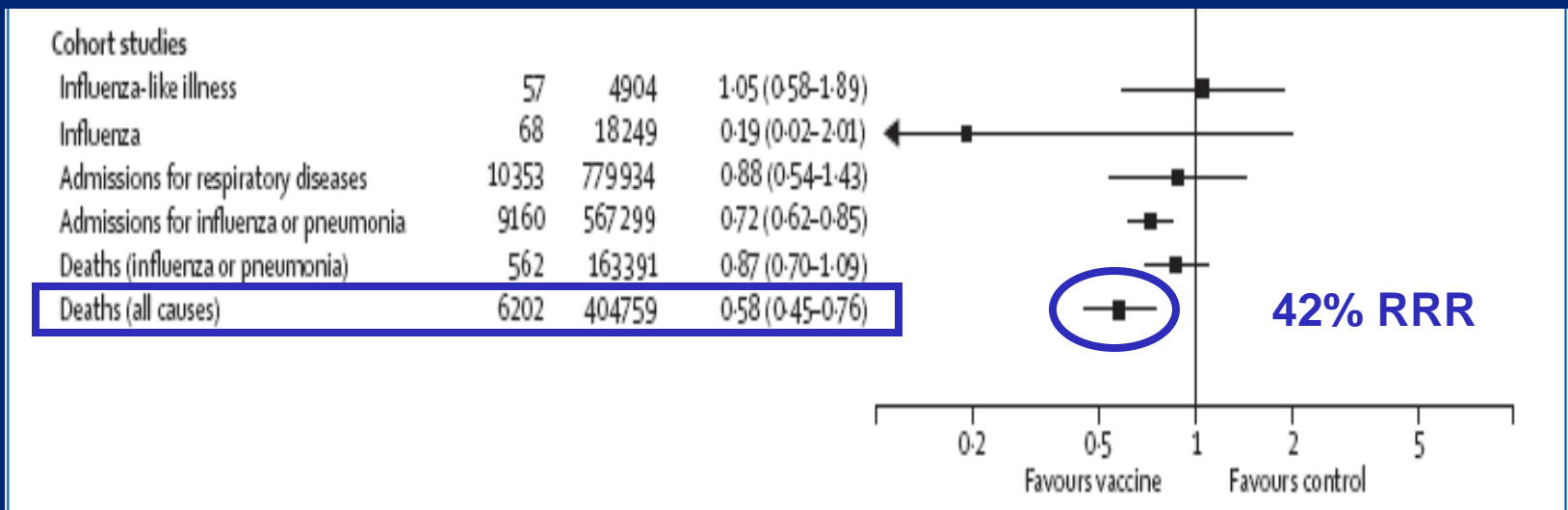
(Govaert et al. JAMA. 1994;272:1661)

Benefits of Flu Jab in the Elderly – One High Quality RCT Subgroup (n=544)



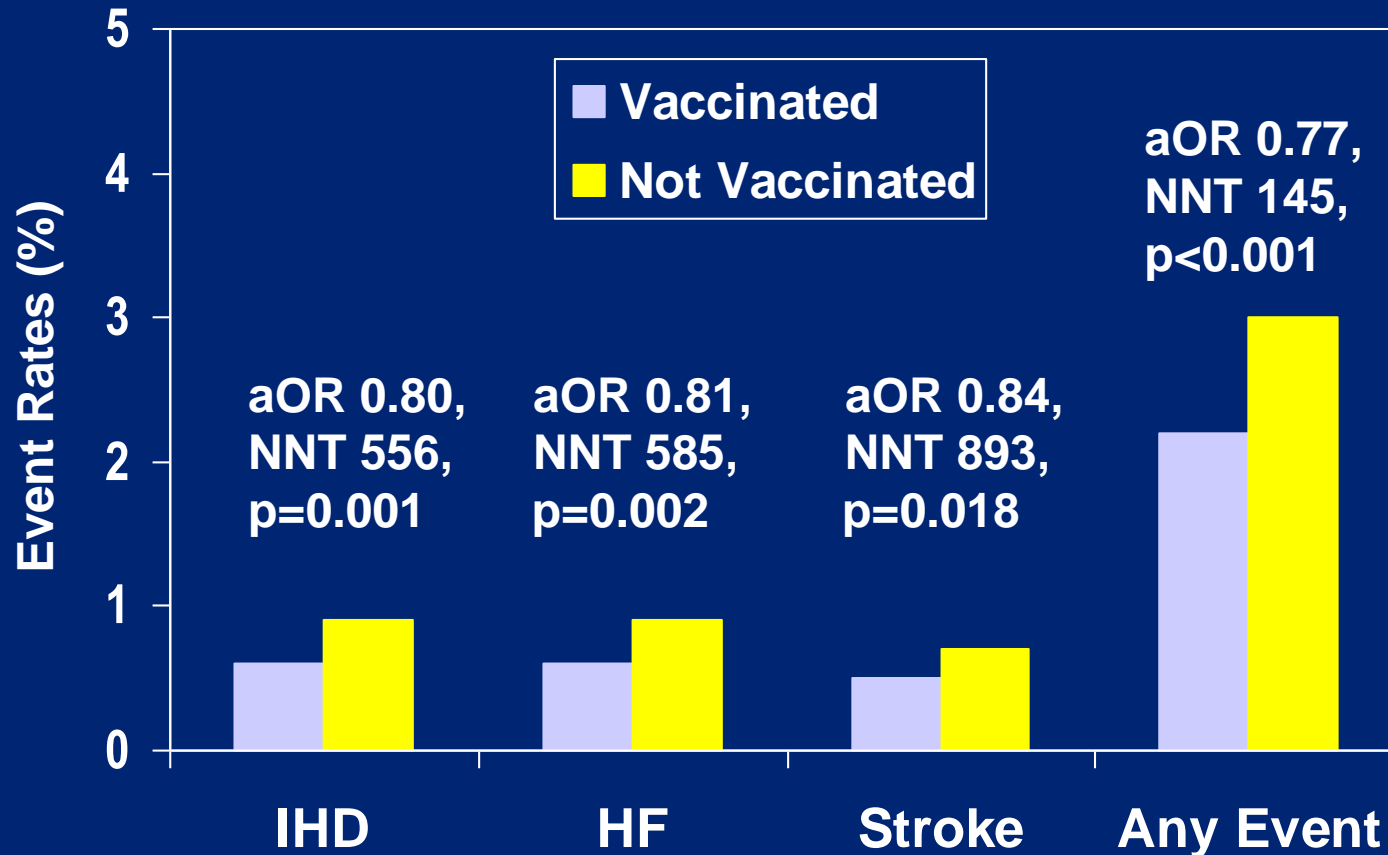
(Govaert et al. JAMA. 1994;272:1661)

Meta-Analysis of All Non-Randomized Studies of Flu Vaccine Effectiveness



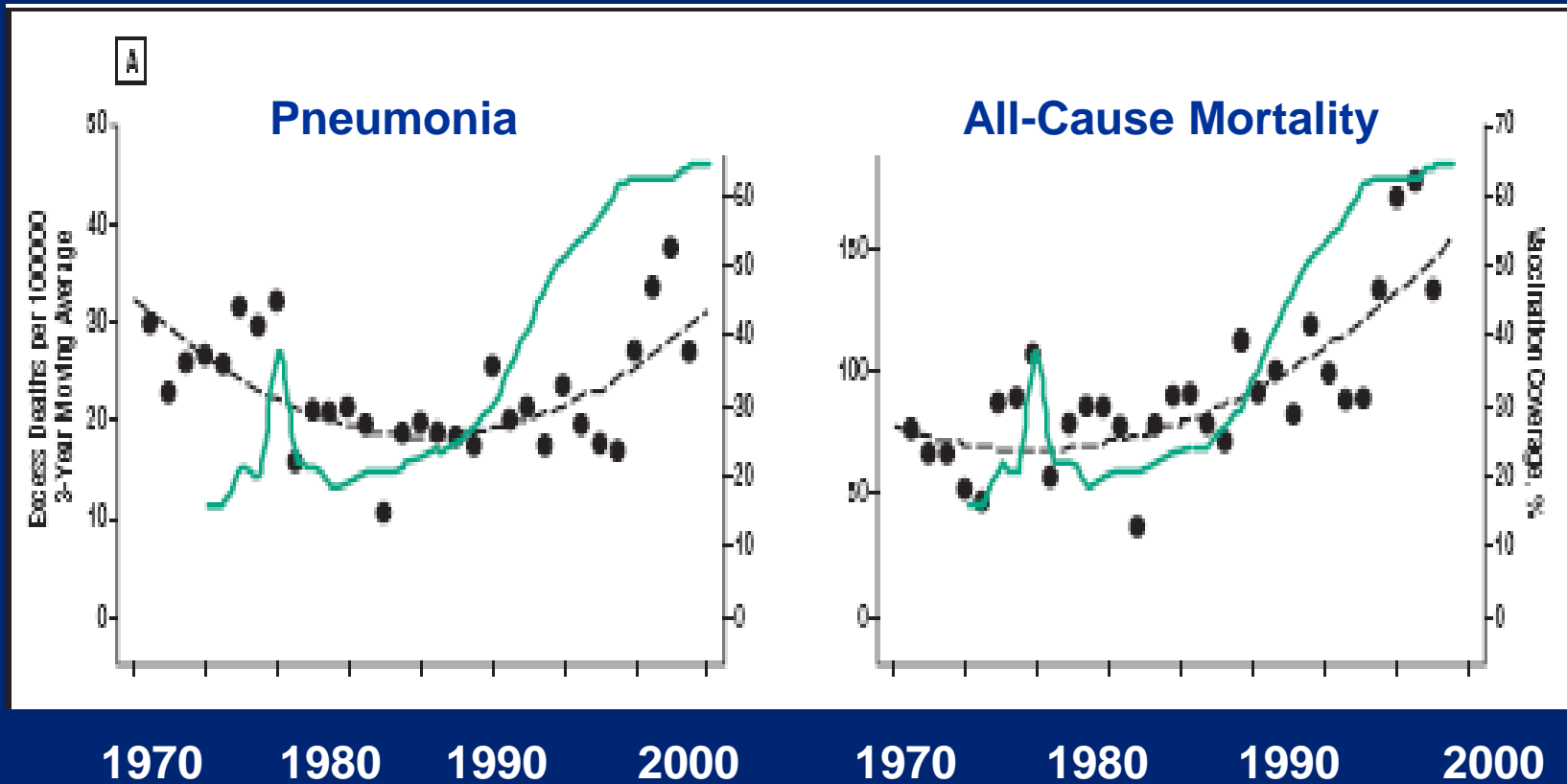
(Jefferson et al. Lancet. 2007;370:1199 and replicated in definitive cohort study [n=18 cohorts, 700k person-years] by Nichol et al. N Engl J Med. 2007;357:1373)

“Pleiotropic” Benefits of Flu Vaccine



(Nichol et al. N Engl J Med. 2003;348:1322)

Vaccination Rates in the Elderly Have Increased Four-Fold Since 1980



(Simonsen et al. Arch Int Med. 2005;165:265)

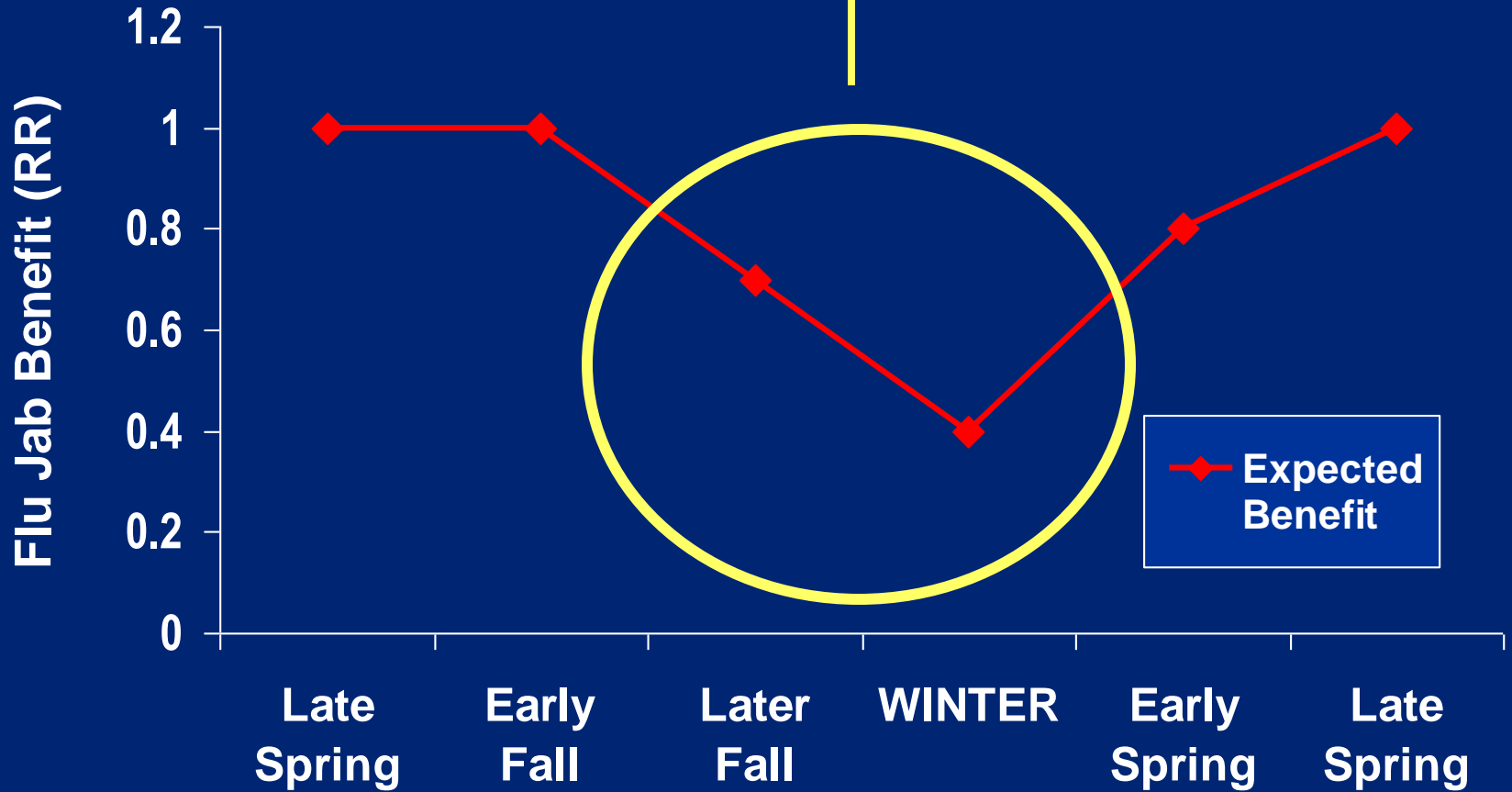
In summary (ii)

- 1. Flu vaccine has small to absent clinical benefit in randomized trials**
- 2. Stable or increasing pneumonia and death rates in the elderly in the face of 400% increases in vaccine coverage**
- 3. But flu vaccine has a huge benefit in every cohort ever studied and published (*until recently*)**

Design of Most Cohort Studies of Flu Vaccine Effectiveness?

- ✓ Population-based samples of community dwelling elderly
- ✓ Exposure = flu vaccination
- ✓ Outcome = all-cause mortality
- ✓ Administrative or claims type data, risk adjustment based on ICD codes
- ✗ Little info re: healthy-vaccinee effects (smoking, function, meds, adherence)
- ✗ Analysis restricted to influenza season

Analyses restricted to flu season since no expected benefit when no flu present

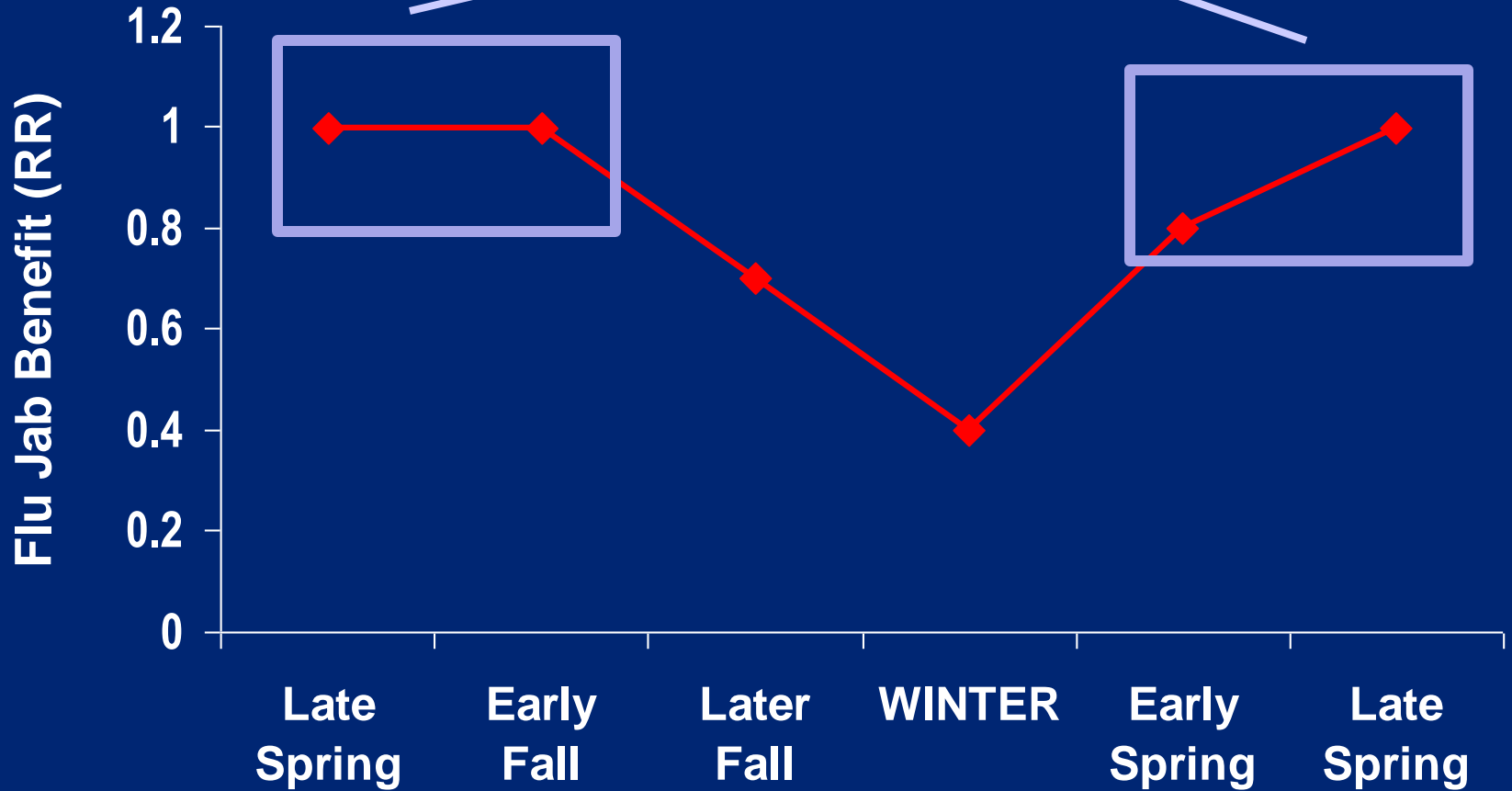


(Simonsen et al. Lancet. 2007;7:658)

Alternate Study Design for Examining Flu Vaccine Benefits

- ✓ Population-based samples of community dwelling elderly
- ✓ Exposure = flu vaccination
- ✓ Outcome = all-cause mortality
- ✓ Administrative or claims type data, risk adjustment based on ICD codes
- ✓ Rich info re: healthy-vaccinnee effects (smoking, function, meds, adherence)
- ✓ Analysis restricted to the off-season

Analyses restricted to off-season since no expected benefit when no flu present



(Simonsen et al. Lancet. 2007;7:658)

Analytic Approach Using A Population-Based Clinical Registry

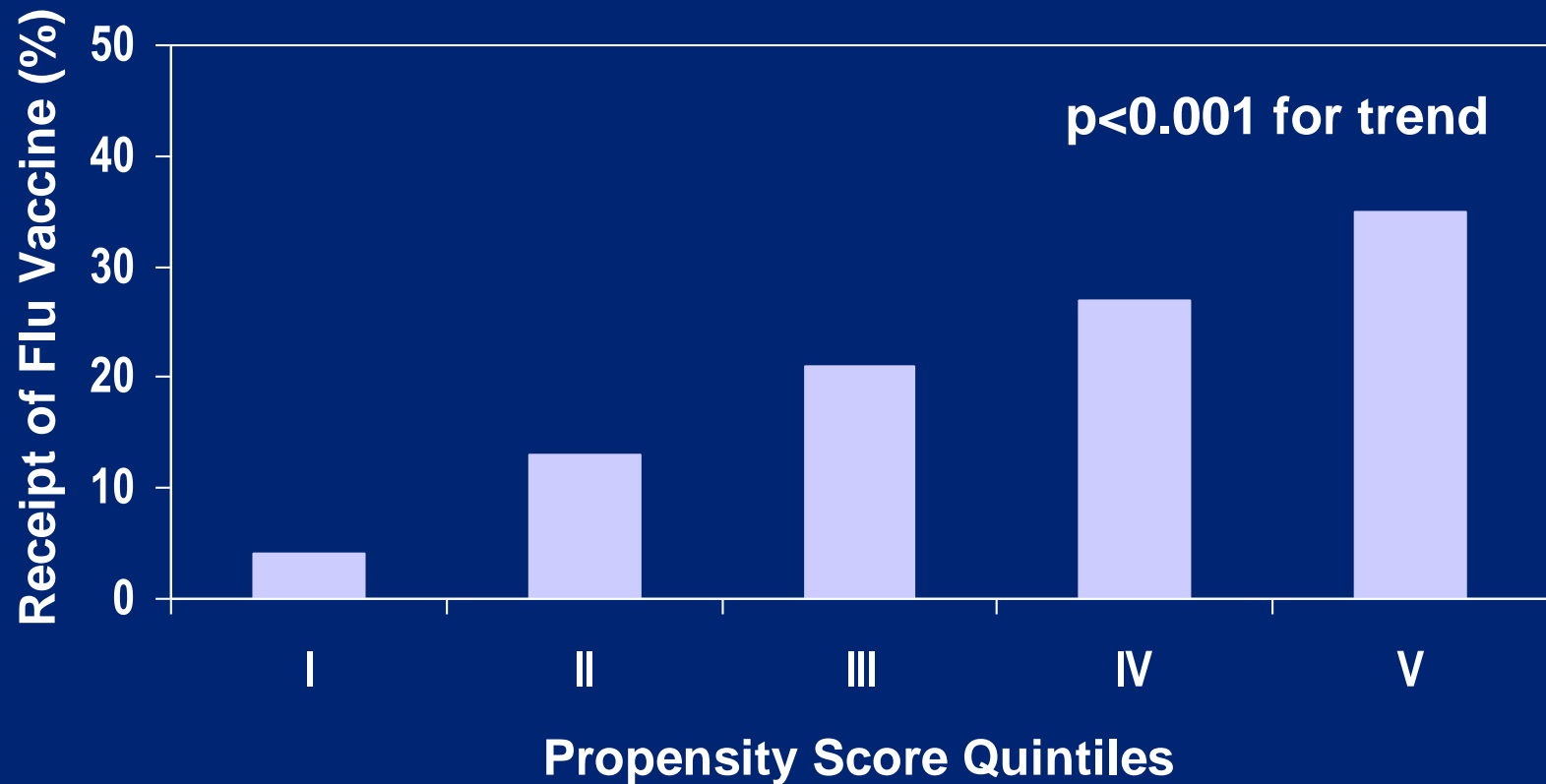
- **Excluded patients with pneumonia admitted during the influenza season(s)**
- **Created propensity (to be vaccinated) score using 36 variables – c-statistic = 0.91**
- **1:1 propensity score matched and covariate-balanced every flu vaccine recipient with an unvaccinated control**
- **Multivariable logistic regression**

Flu Jabs in ~3500 Patients With Pneumonia

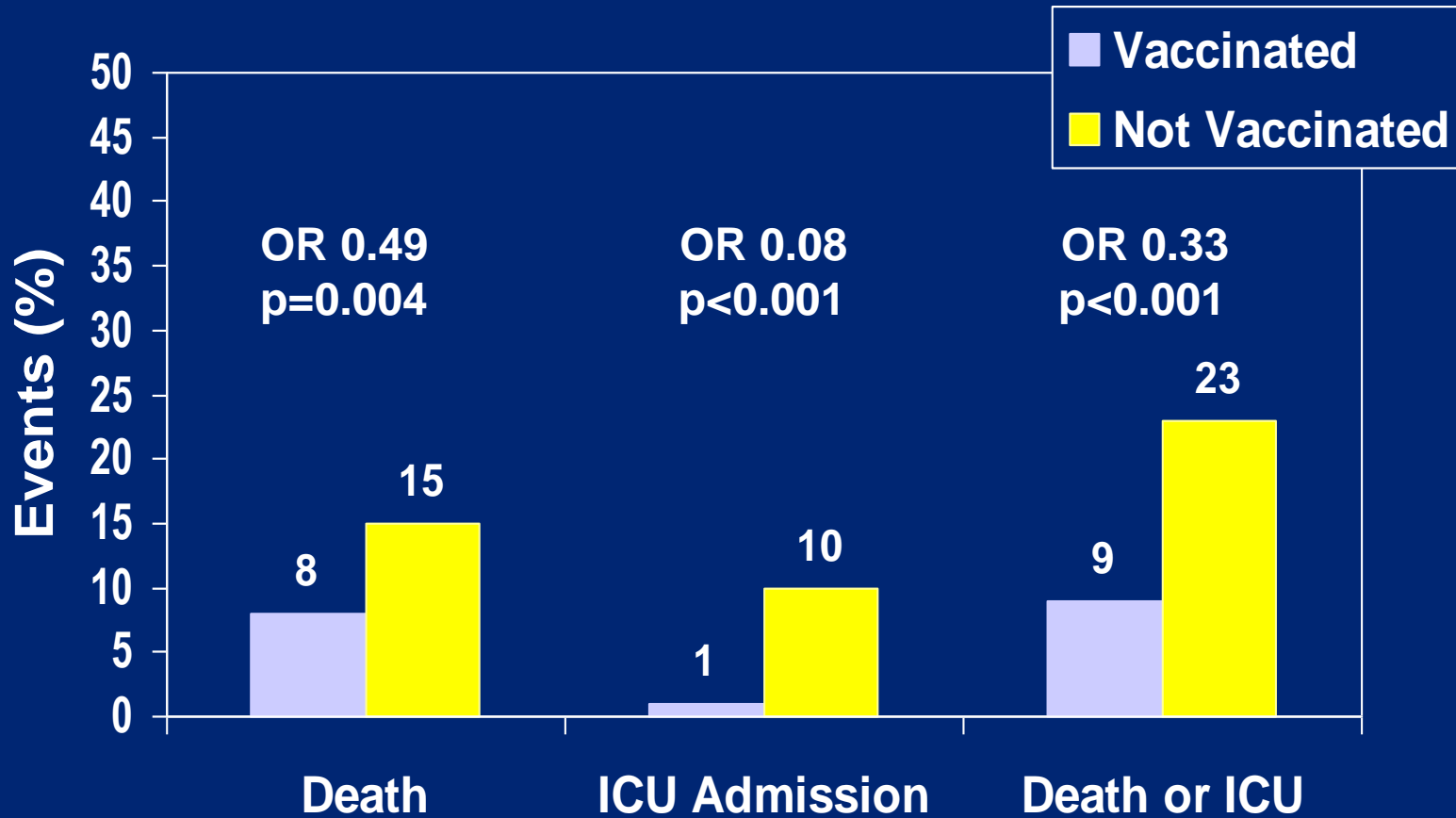
– Differences in Rarely Captured Data

<i>Characteristics</i>	Flu Jabs	NO Jabs	P-value
More than 5 regular meds	23%	14%	<0.001
Statin user	35%	25%	<0.001
Former smoker	42%	30%	<0.001
Independent in mobility	97%	92%	0.02
Advanced directive in place	18%	9%	<0.001
Etcetera	-	-	-

Receipt of Flu Vaccine According to Quintiles of Propensity Score



Adverse Events in the Spring and Summer, According to Flu Vaccination Status



(Eurich et al. Am J Resp Crit Care Med. 2008;178:527)

Sequential Adjustment For Correlates of the Healthy-Vaccinee Effect

All-cause mortality

Unadjusted

0.49

Adjusted for age and sex

0.48

Adjusted for age, sex, nursing home resident, comorbidities, number of medications

0.45

Adjusted for age, sex, nursing home resident, comorbidities, number of medications, PSI

0.52

Adjusted for age, sex, nursing home resident, comorbidities, number of medications, PSI, smoking status, functional status, advanced directive, immunizations, socioeconomic status

0.81

Odds Ratio:

0.2 0.4 0.6 0.8 1 1.2 1.4 1.6 1.8 2

Reduced Risk

Increased Risk

“pleiotropic”
benefits

“Pleiotropic” Benefits or Refractory Confounding ?

	Fully Adjusted OR (95%CI)	p-value
Death	0.81 (0.35-1.85)	0.6
ICU Admission	0.17 (0.04-0.71)	0.014
Death or ICU	0.50 (0.25-1.00)	0.05

(Eurich et al. Am J Resp Crit Care Med. 2008;178:527)

In summary (iii)

- 1. There is no plausible mechanism for benefits of flu vaccine in absence of flu**
- 2. Suggests that the mortality benefit of flu vaccine in the elderly in prior studies vastly and systematically over-estimated**
- 3. More broadly, even with rich clinical data it is difficult if not impossible to control for presence of the healthy-user effect**

Conclusions

- **Non-randomized studies reporting “unanticipated” benefits of treatment should be interpreted with great caution**
- **Confounding by the healthy-user effect is ubiquitous and often a better or alternate explanation for unanticipated benefits**
- **The healthy-user effect probably cannot be controlled without randomized trials (or very rich clinical data)**

Questions or Comments?

