Bayesian model averaging in Meta-analysis: Vitamin E supplementation and Mortality

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Outline

- Introduction and Background
- Study Selection
- Data
- Model
- Results
- Conclusions

Introduction

- In the United States, the most commonly used dietary supplements are multivitamin and mineral supplements
- Many recent studies examined safety
- Each study contributes to our knowledge of how the supplements work
- Three recent meta-analyses examined the relationship between dose of vitamin E and mortality
  - Different conclusions - “high dose”

Meta-Analysis?

- Combine results from multiple clinical trials
  - Do not have individual patient data
  - Not all studies collect the same information
  - Not all studies have the same patient population
  - Difficult to interpret traditional confidence intervals from each study
  - Trial effect
- Must consider trial effect
- Dose response
  - Linear, quadratic, spline, others or no effect

Study Selection

- Random allocation of patients
- Vitamin E supplementation alone or with other vitamins or minerals
- Use of control or placebo group
- Participants were men and non-pregnant women
- Follow-up of one year and ten or more deaths

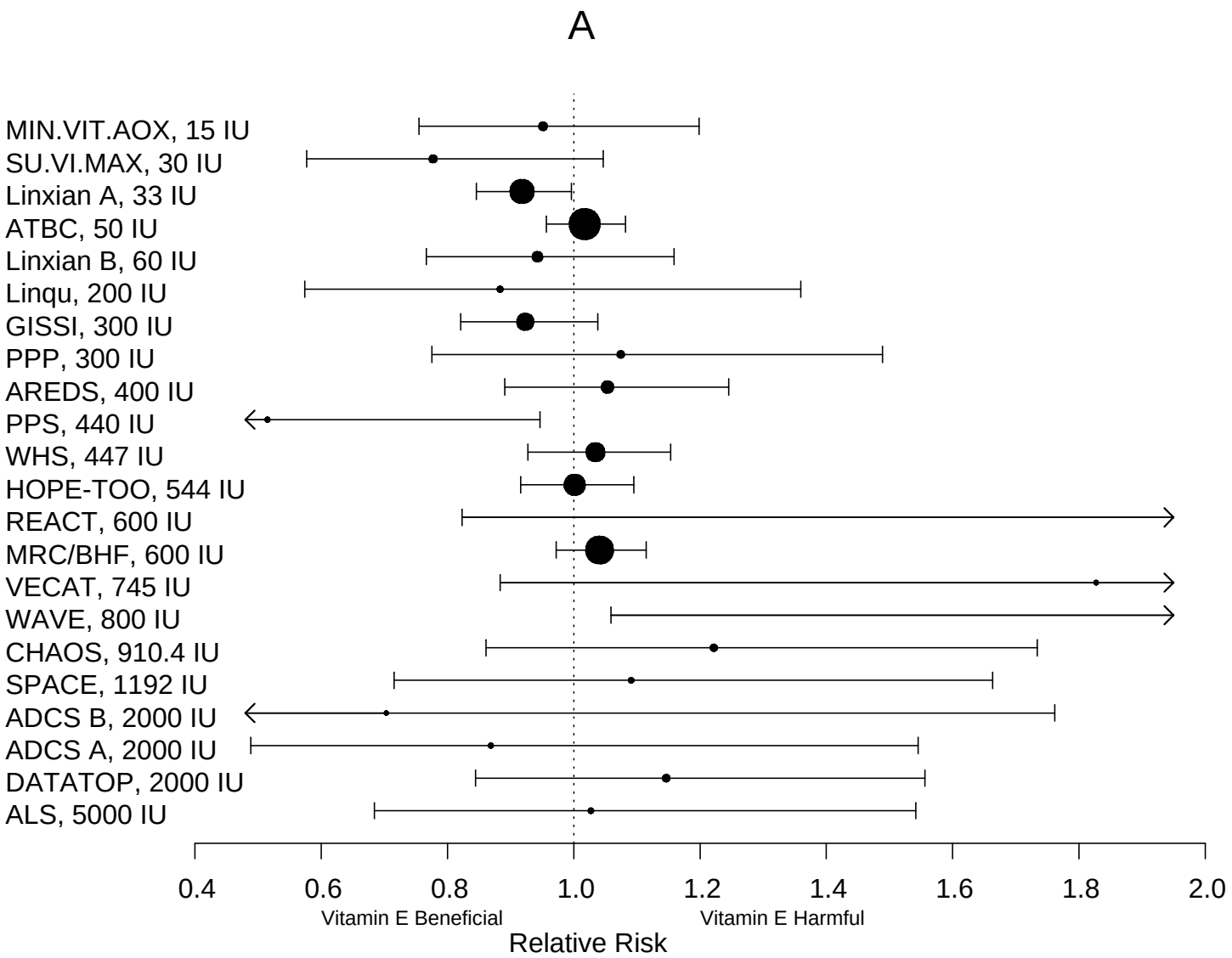
Data

- 22 studies (extracted from 24 publications)
- Intent to treat N ranged from 160 to 29,584
- Data discrepancies were resolved by contacting the authors of the original studies
  - Numbers for intent-to-treat patients
  - Milligrams or IU
  - Various forms of vitamin E
- Converted all units into IU
  - A previous meta-analysis failed to do this

Model

- We consider the death rate π
  - It may differ from one study to another even if patients have the same clinical characteristics and receive the same treatment
- Cannot simply combine the data as if it comes from one large study
- Bayesian hierarchical model used to allow different π values in different studies

Each Study Independent -95% CI



Vitamin E Dose-π Relationship

- Covariates
  - E was used in combination with other vitamins or minerals, mean subject age, sex, and follow-up duration
- Quadratic-linear (used in previous meta-analysis analysis)
- Linear
- Quadratic
- No vitamin E effect

Hierarchical Model

Denote the mortality rate on study i for S and E by $\pi_{S,i}$ and $\pi_{E,i}$, respectively, D_i = Dose of study i, Z_i denotes the covariate of interest

$$\delta_i = \pi_{E,i} - \pi_{S,i}$$

$$\delta_i = N(\mu_{\delta(Di,\, Zi)},\ \sigma^2)$$

Mean Structure $\mu_{\delta(Di,\ Zi)}$

Model	$m_d(D_i, Z_i)$[a]	Description
2	$\alpha_0+\beta_0 D_i$	Linear dose effect, no covariate effect
3	$\alpha_0+ \beta_0 D_i+\zeta_0 D_i^2$	Quadratic dose effect, no covariate effect
4	$\alpha_0+ \beta_0 D_i+ \beta_1 D_i Z_i$	Linear dose effect with different slope for each covariate group
5	$\alpha_0+ \beta_0 D_i+ \alpha_1 Z_i$	Linear dose effect with different intercept for each covariate group
6	$\alpha_0+ \beta_0 D_i+ \alpha_1 Z_i+ \beta_1 D_i Z_i$	Linear dose effect with different slope and intercept for each covariate group
7	$\alpha_0+ \beta_0 D_i+ \zeta_0 D_i^2+ \alpha_1 Z_i$	Quadratic dose effect, treatment covariate interaction
8	$\alpha_0+ \beta_0 D_i+ \zeta_0 D_i^2+ \beta_1 D_i Z_i$	Quadratic dose effect, treatment covariate interaction
9	$\alpha_0+ \beta_0 D_i+ \zeta_0 D_i^2+ \zeta_1 D_i^2 Z_i$	Quadratic dose effect, treatment covariate interaction
10	$\alpha_0+ \beta_0 D_i+ \zeta_0 D_i^2+ \alpha_1 Z_i+ \beta_1 D_i Z_i$	Quadratic dose effect, treatment covariate interaction
11	$\alpha_0+ \beta_0 D_i+ \zeta_0 D_i^2+ \alpha_1 Z_i+ \zeta_1 D_i^2 Z_i$	Quadratic dose effect, treatment covariate interaction
12	$\alpha_0+ \beta_0 D_i+ \zeta_0 D_i^2+ \beta_1 D_i Z_i+ \zeta_1 D_i^2 Z_i$	Quadratic dose effect, treatment covariate interaction
13	$\alpha_0+ \beta_0 D_i+ \zeta_0 D_i^2+ \alpha_1 Z_i+ \beta_1 D_i Z_i+ \zeta_1 D_i^2 Z_i$	Quadratic dose effect, treatment covariate interaction

[a] D_i is the dose of trial i; Z_i is the covariate for trial i.

Priors

σ^2 controls the amount of "borrowing" across studies

- ***Large values of σ^2 will borrow less***
- ***Small values borrow more***
- ***Need sensitivity analysis***

All other priors are normal, uninformative

Model Averaging

- Typical approach would be to do model criticism, pick the model that fit “best,” and provide results
- Model averaging
  - Allow for the possibility of a zero vitamin E effect
  - Avoid throwing out models that are not the “best”
- Average across mean structures based on the posterior model probability

Prior Model Probabilities

Model Dose-Response Relationship	Prior Probability
No E Effect	0.25
Spline	0.25
Linear	0.25
Quadratic	0.25

Results

Model	Dose (IU)	95% PCI Contains No E Effect	No Effect	Beneficial	Harmful
Spline	200	Yes	0	0.20	0.80
	400	Yes	0	0.16	0.84
	800	Yes	0	0.14	0.86
	1600	Yes	0	0.18	0.82
Linear	200	Yes	0	0.67	0.33
	400	Yes	0	0.57	0.43
	800	Yes	0	0.34	0.66
	1600	Yes	0	0.22	0.78
Quadratic	200	Yes	0	0.78	0.22
	400	Yes	0	0.46	0.54
	800	Yes	0	0.14	0.86
	1600	Yes	0	0.08	0.91

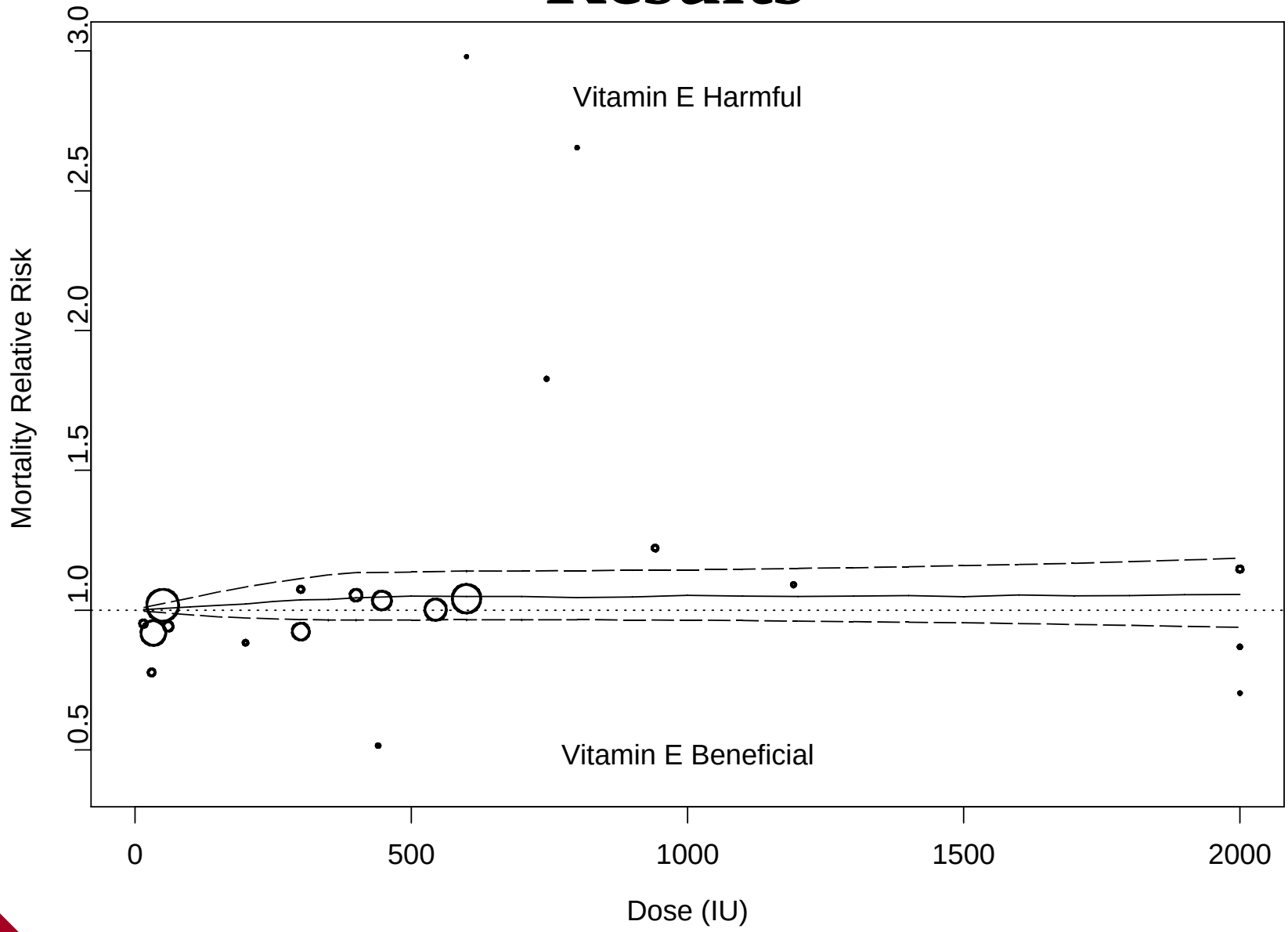
Posterior Model Probabilities

Model Dose-Response Relationship	Prior Probability	Posterior Probability
No E Effect	0.25	0.94
Spline	0.25	0.04
Linear	0.25	0.02
Quadratic	0.25	<0.01

Posterior Model Probabilities

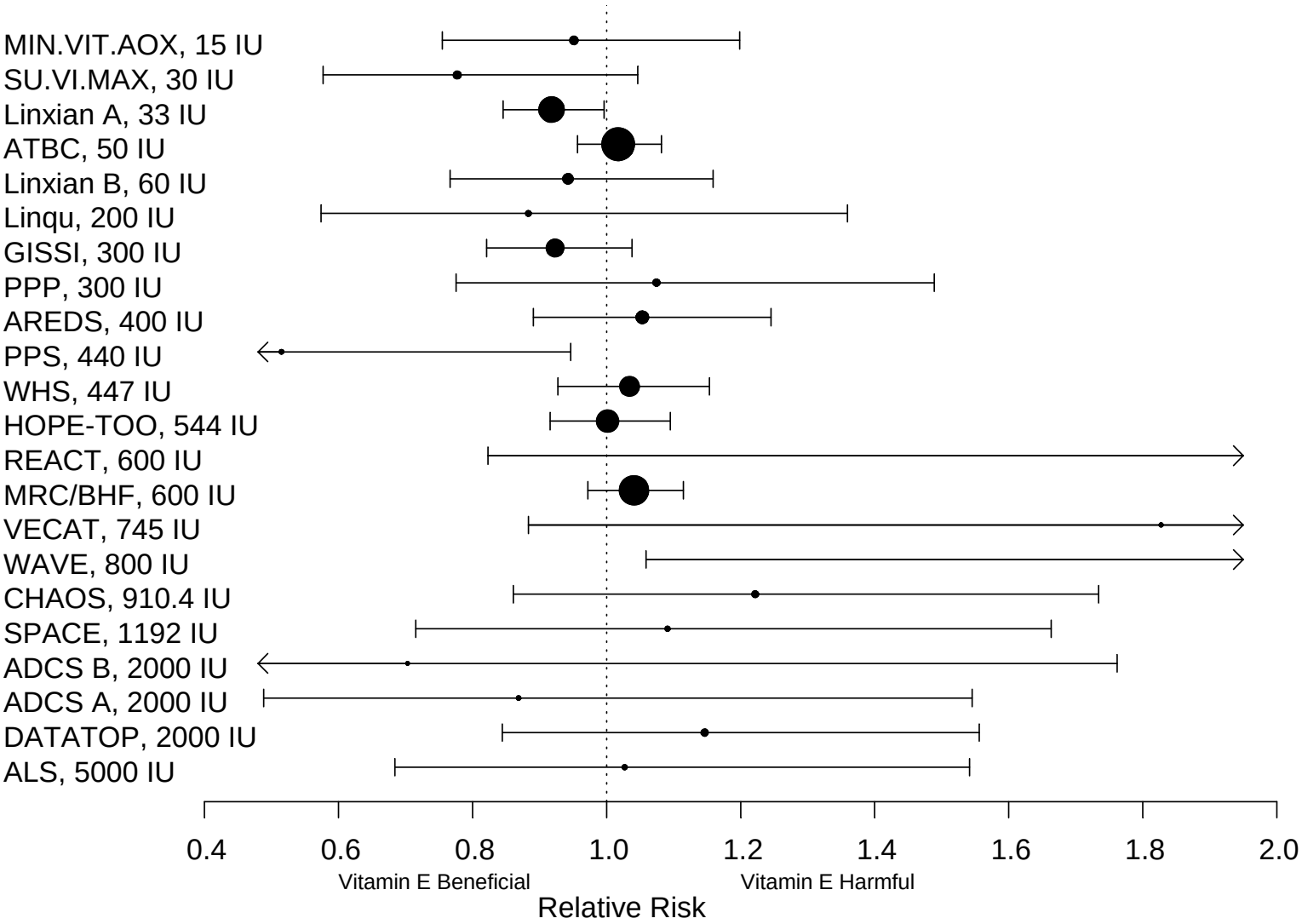
Model Dose-Response Relationship	Prior Probability	Posterior Probability
No E Effect	0.01	0.92
Spline	0.33	0.06
Linear	0.33	0.02
Quadratic	0.33	<0.01

Results


Vitamin E Harmful
Vitamin E Beneficial
Mortality Relative Risk
3.0
2.5
2.0
1.5
1.0
0.5
0
500
1000
1500
2000
Dose (IU)

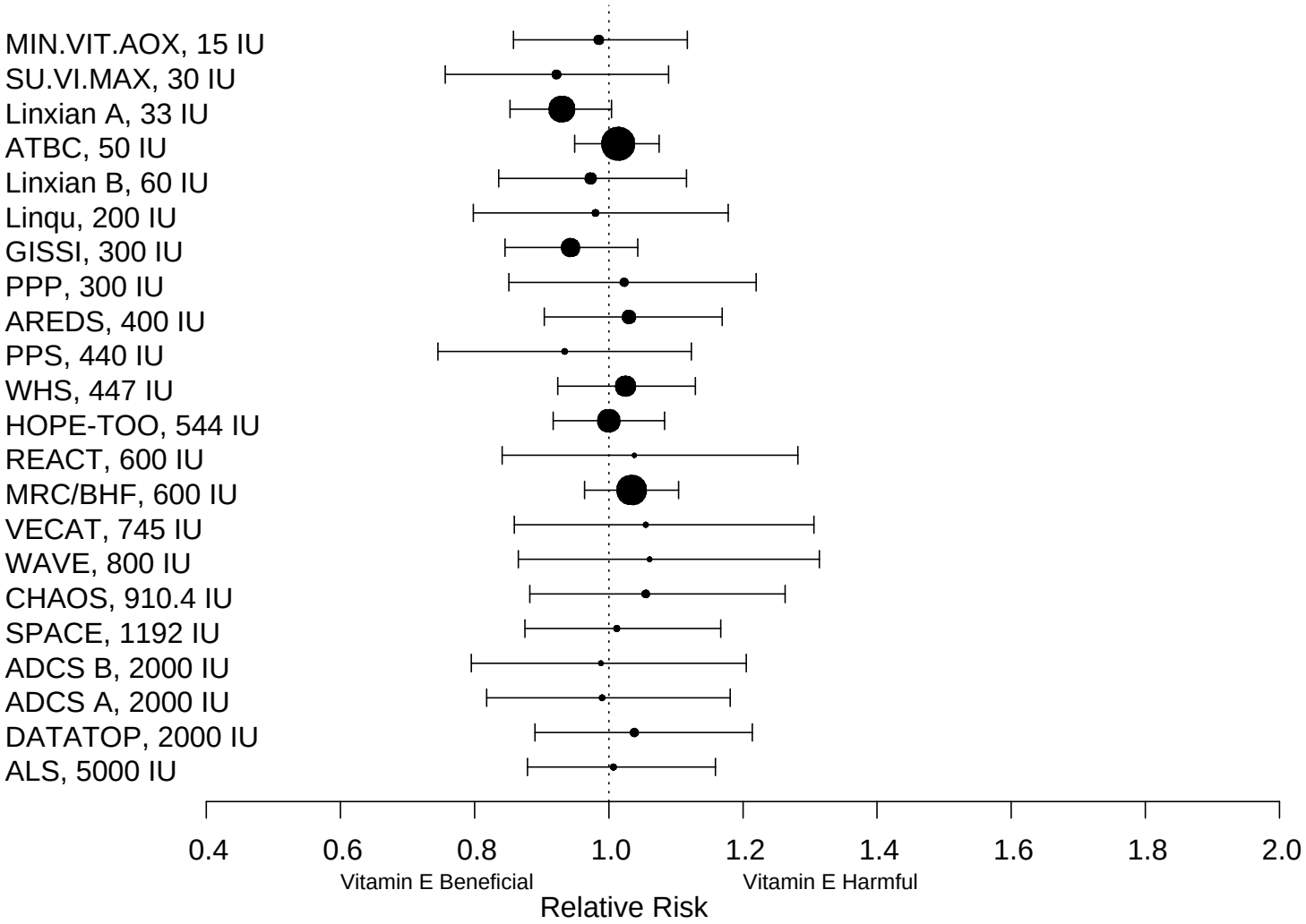
Independent Studies, 95% CI

A



Results

B


MIN.VIT.AOX, 15 IU
SU.VI.MAX, 30 IU
Linxian A, 33 IU
ATBC, 50 IU
Linxian B, 60 IU
Linqu, 200 IU
GISSI, 300 IU
PPP, 300 IU
AREDS, 400 IU
PPS, 440 IU
WHS, 447 IU
HOPE-TOO, 544 IU
REACT, 600 IU
MRC/BHF, 600 IU
VECAT, 745 IU
WAVE, 800 IU
CHAOS, 910.4 IU
SPACE, 1192 IU
ADCS B, 2000 IU
ADCS A, 2000 IU
DATATOP, 2000 IU
ALS, 5000 IU
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
Vitamin E Beneficial
Vitamin E Harmful
Relative Risk

Sensitivity of σ^2

Heterogeneity	No Vitamin E Effect	Vitamin E Beneficial	Vitamin E Harmful
Least (most homogeneous)	0.948	0.015	0.037
Very little	0.945	0.032	0.037
Little	0.944	0.034	0.038
Moderate	0.943	0.019	0.038
High	0.942	0.021	0.039
Highest [a]	0.940	0.020	0.040

Conclusions

- Using a data-derived average of the various candidate models more accurately reflects the uncertainty that is present in the data
- Our model averaging approach is not dependent on any particular model and so gives rise to substantially less precision
- Less sensitive to local fluctuations in the observed dose-response relationship
- At a dose less than 1600 IUs unlikely to affect all-cause mortality