

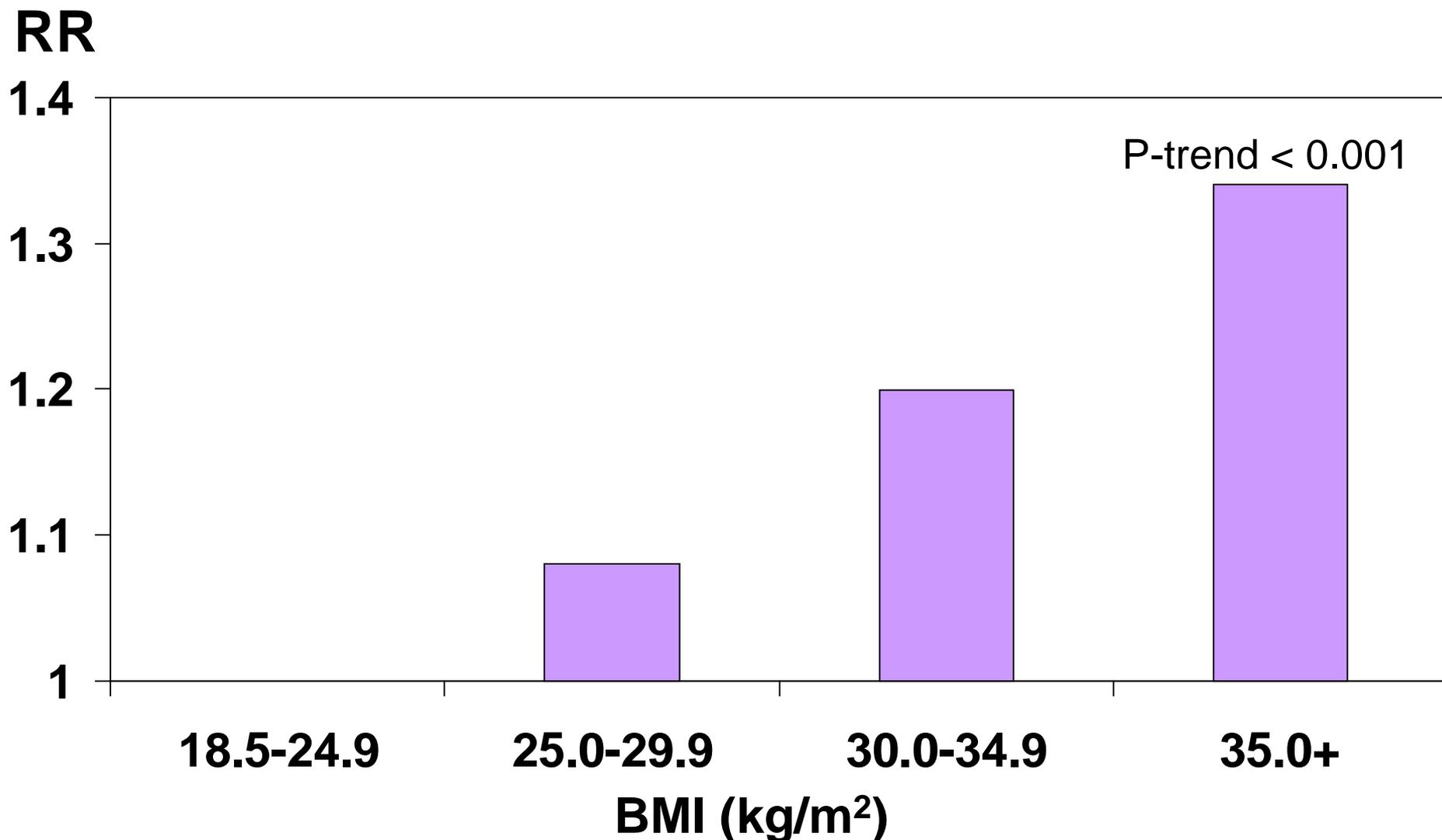
# **Evidence for the role of obesity in prostate cancer progression**

**Elizabeth A. Platz, ScD, MPH**

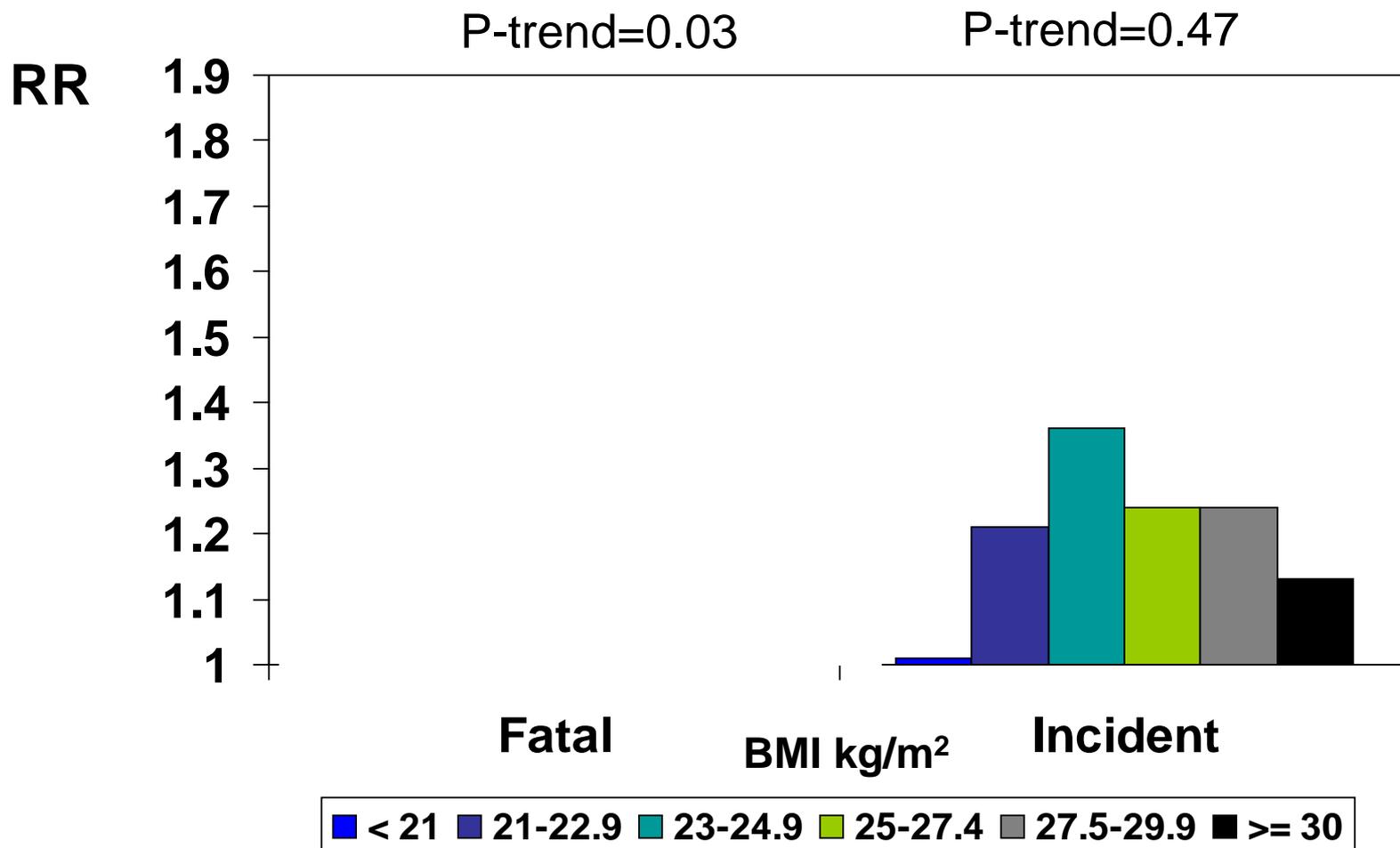
Professor and Martin D. Abeloff, MD Scholar in Cancer Prevention  
Johns Hopkins Bloomberg School of Public Health and  
the Sidney Kimmel Comprehensive Cancer Center  
at Johns Hopkins

# **Quick update on body fatness and prostate cancer incidence and mortality**

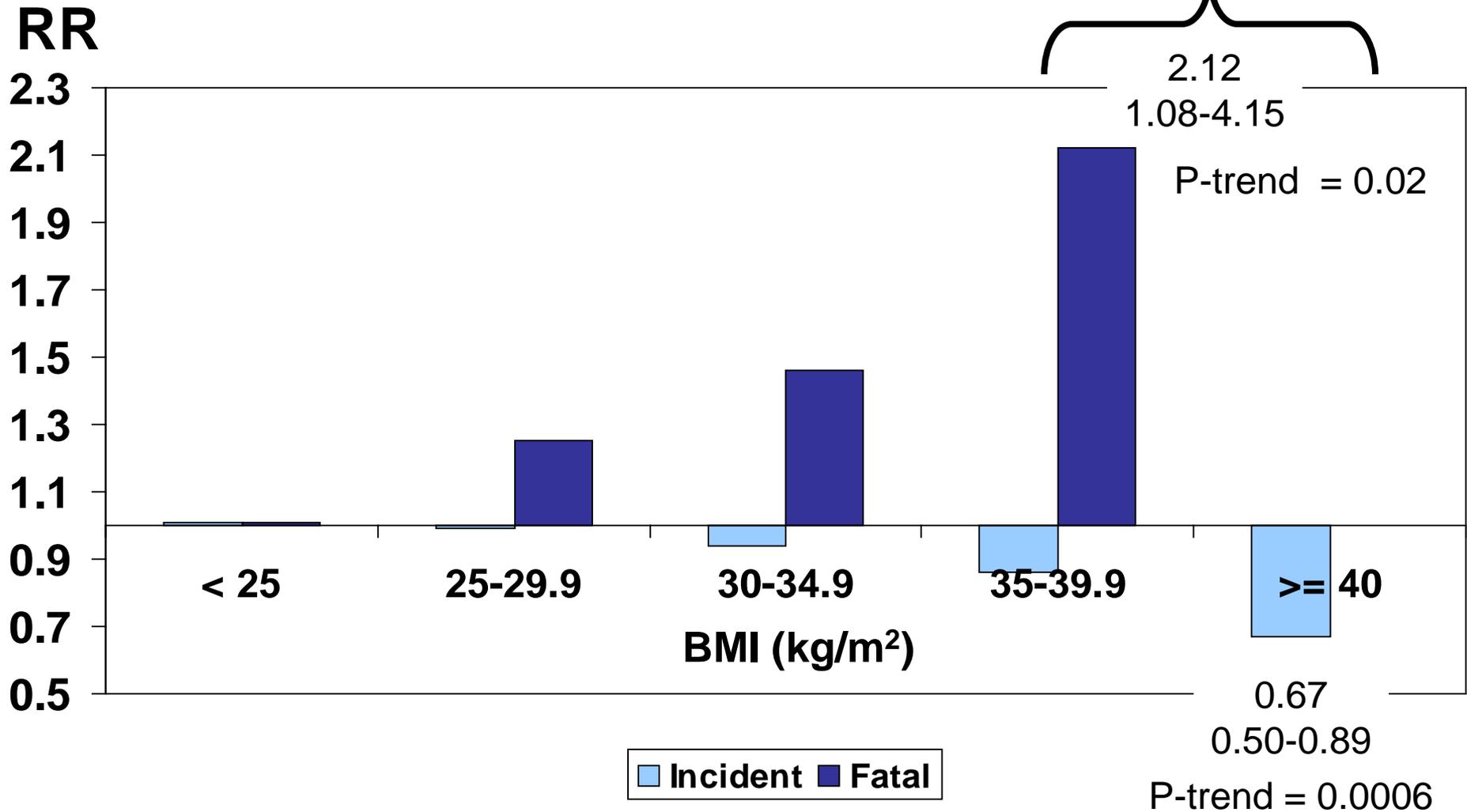
# Death from prostate cancer by BMI, Cancer Prevention Study II, 1982-1998



# Obesity and prostate cancer, Health Professionals Follow-up Study



# Obesity and prostate cancer risk in the NIH-AARP Diet and Health Study



# Cause versus bias?

- *Obesity*®
  - Risk (causation)
    - - Risk of death from prostate cancer
    - - Risk of nonaggressive prostate cancer
  - Detection bias
    - - PSA (lower production, hemodilution)
    - - Prostate volume

# What about obesity / weight gain and poor outcome after prostate cancer diagnosis?

- Emerging support that the extent of body fatness and weight gain
  - Before diagnosis
  - Circa diagnosis
- are risk factors for recurrence and prostate cancer death in men with prostate cancer.
- Excellent review: Cao Y and Ma J. Cancer Prev Res 2011;4:486-501. PMID: 21233290.

# **Considerations (fully or partially) specific to prostate cancer outcomes**

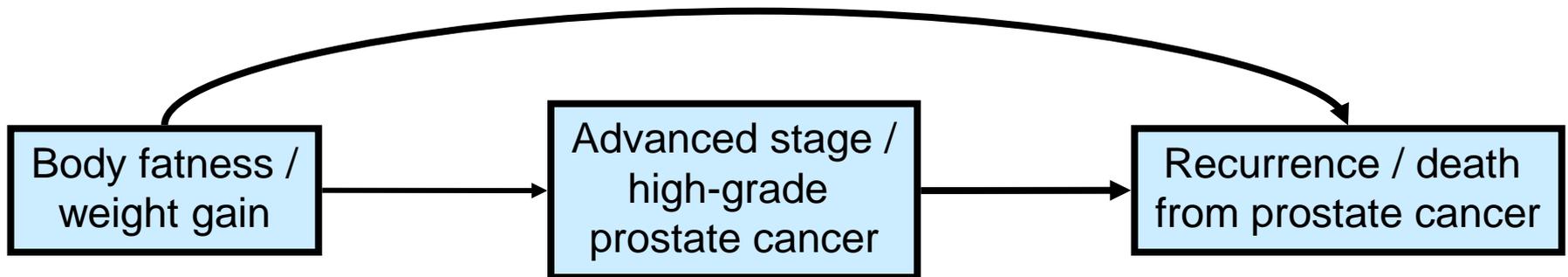
- To confirm or refute associations observed thus far
- For studies going forward

# Consideration 1

- What is the optimal prostate cancer outcome to capture biology and import?
  - Biology and import: Progression to metastasis or death from prostate cancer.
  - Nature of outcome that can be studied may depend on the type of treatment, though.
    - Especially when studying men with clinically localized prostate cancer (patients selected for curability ® few deaths)
      - Surgery - biochemical recurrence
      - Radiation therapy or active surveillance - rising PSA

## Consideration 2

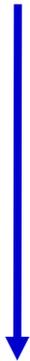
- Confounding - Body fatness appears to be a risk factor for advanced stage and high-grade prostate cancer AND stage/grade are prognostic factors
  - Must take into account stage and grade in the analysis to determine whether body fatness/weight gain are associated with poor outcome in men with prostate cancer



# Consideration 3

- Etiologically relevant measurement - Timing of body fatness / weight gain relative to the diagnosis / treatment of prostate cancer
  - Pre-diagnostic
  - At diagnosis / treatment
  - Post diagnosis / treatment

Body fatness /  
weight gain



Body fatness /  
weight gain



Body fatness /  
weight gain



Body fatness /  
weight gain

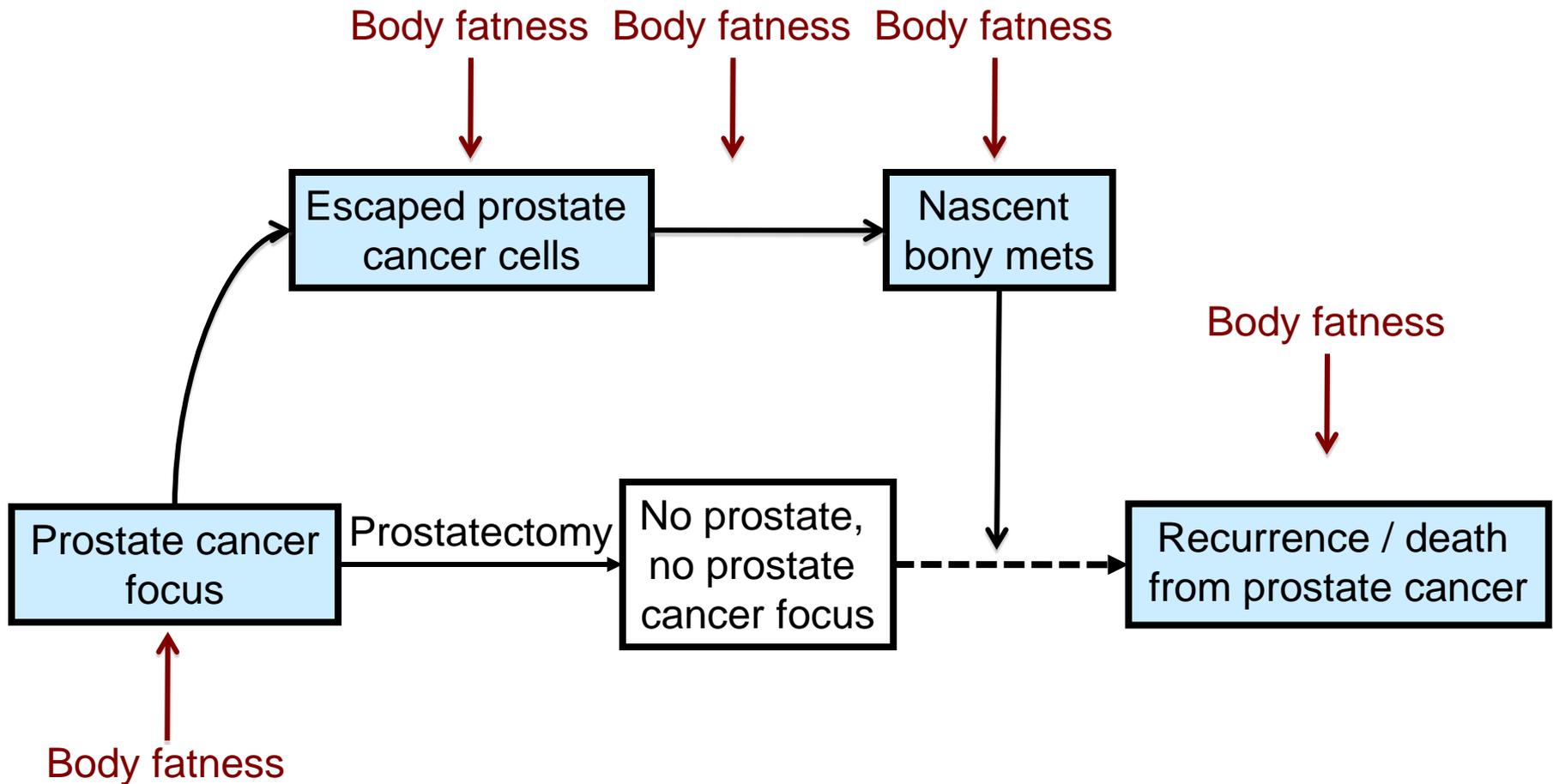


Normal → Precursors →

Prostate cancer



# How can body fatness influence outcomes after treatment, especially after prostatectomy?

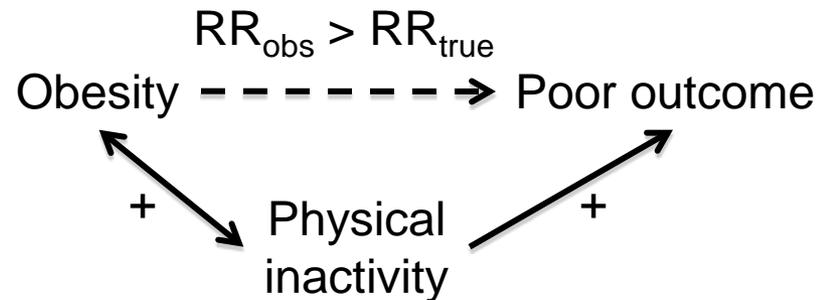


# Consideration 4

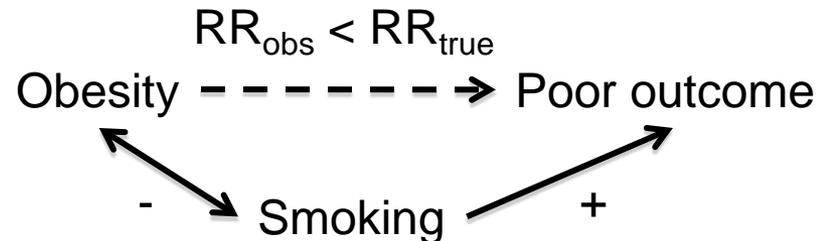
- Does the influence of weight gain on outcome differ by starting body fatness?
  - Lean, gain weight
  - Obese, gain weight
  - Lean, no weight gain
  - Obese, no weight gain
- Considerations 3 and 4 coupled: Full evaluation of body fatness and weight gain over the life course.
  - Requires prospective study of men without the diagnosis, followed to diagnosis (and treatment), and then followed to death
  - Requires repeated measures of body fatness, including circa the diagnosis /treatment

# Consideration 5

- Confounding and modifying effects by factors that are highly correlated with body fatness
  - Physical inactivity
  - Diabetes
  - Energy intake
  - Smoking



- Statistical analyses



# Consideration 6

- Alternative explanations
- Greater technical difficulty when treating obese men relative to lean men (e.g., positive surgical margins)
  - Lower likelihood of cure unrelated to prostate cancer biology
- Different choice of treatment by obese and non-obese men
  - Where the treatment may have a different likelihood of cure irrespective of extent of body fatness
- Won't discuss further today, but needs to be evaluated.

# Consideration 7

- Hormonal therapy for men with metastatic prostate cancer causes central adiposity and metabolic perturbations.
  - What is the influence of this milieu on prostate cancer death (beyond obvious increase in risk of death from other causes)?
- Won't discuss further today, but needs to be evaluated.

# Consideration 8

- Surveillance for the early recurrence (e.g., post-prostatectomy)
  - What is the influence of body fat on PSA produced by cells that have escaped from the prostate?
    - – PSA (lower production, hemodilution) in men who are obese compared with lean
  - Detection bias - time to recurrences would be falsely LONGER in obese compared with lean men
- Won't discuss further today, but needs to be evaluated.

# BMI and risk of biochemical recurrence after prostatectomy, JHH

TABLE 3. RR of time to biochemical progression after RP by BMI relative to normal weight **At the time of surgery**

|   | RR   | 95% CI    | p Value |
|---|------|-----------|---------|
| Adjusting for preop clinical characteristics:*          |      |           | <0.001  |
| Overwt  | 1.50 | 1.14–1.97 |         |
| Mild obesity  | 1.97 | 1.42–2.72 |         |
| Moderate + severe obesity                               | 1.52 | 0.77–3.00 |         |
| Adjusting for clinical + pathological characteristics:† |      |           | 0.03    |
| Overwt  | 1.23 | 0.93–1.62 |         |
| Mild obesity  | 1.51 | 1.09–2.10 |         |
| Moderate + severe obesity                               | 1.29 | 0.65–2.54 |         |

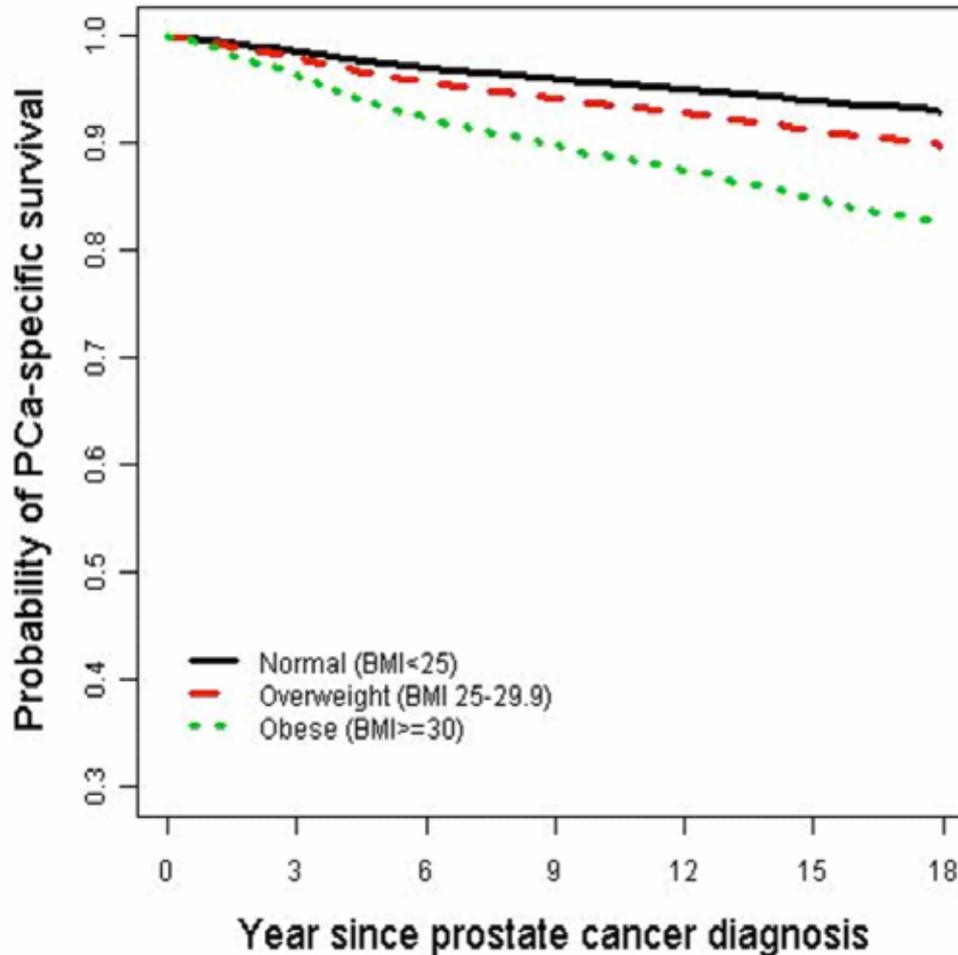
\* Age, race, biopsy Gleason sum, clinical stage, preoperative PSA and year of surgery.

† Age, race, clinical stage, preoperative PSA, year of surgery, pathological Gleason sum, margin status, extraprostatic extension, seminal vesicle invasion and lymph node metastasis.

Covariates

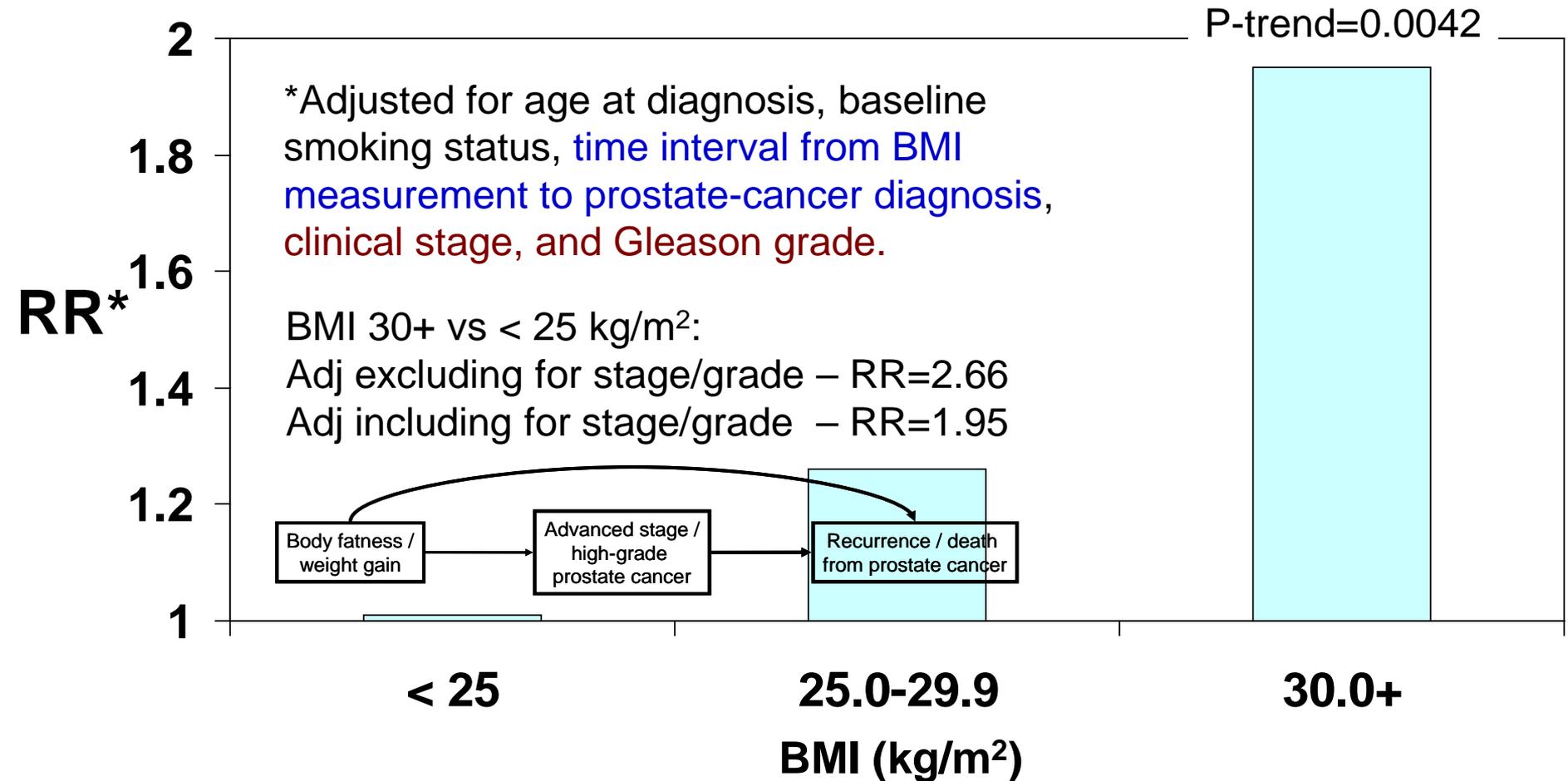
# Pre-diagnostic obesity and prostate cancer death in men with prostate cancer, Physicians' Health Study

**A. Baseline BMI: Overall study period 1982-2007**

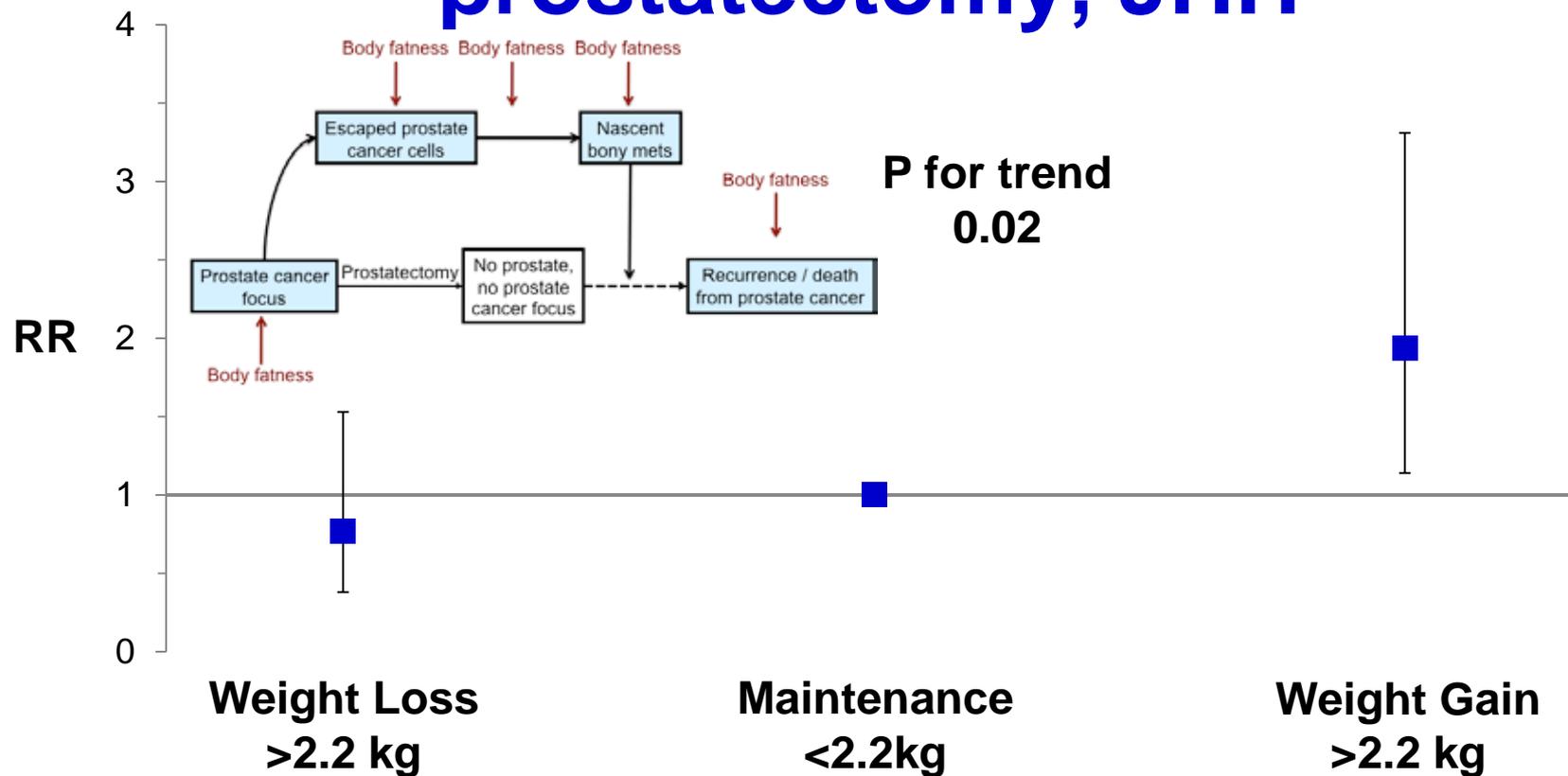


**Unadjusted**

# Pre-diagnostic body mass index and prostate cancer death in men with prostate cancer, PHS



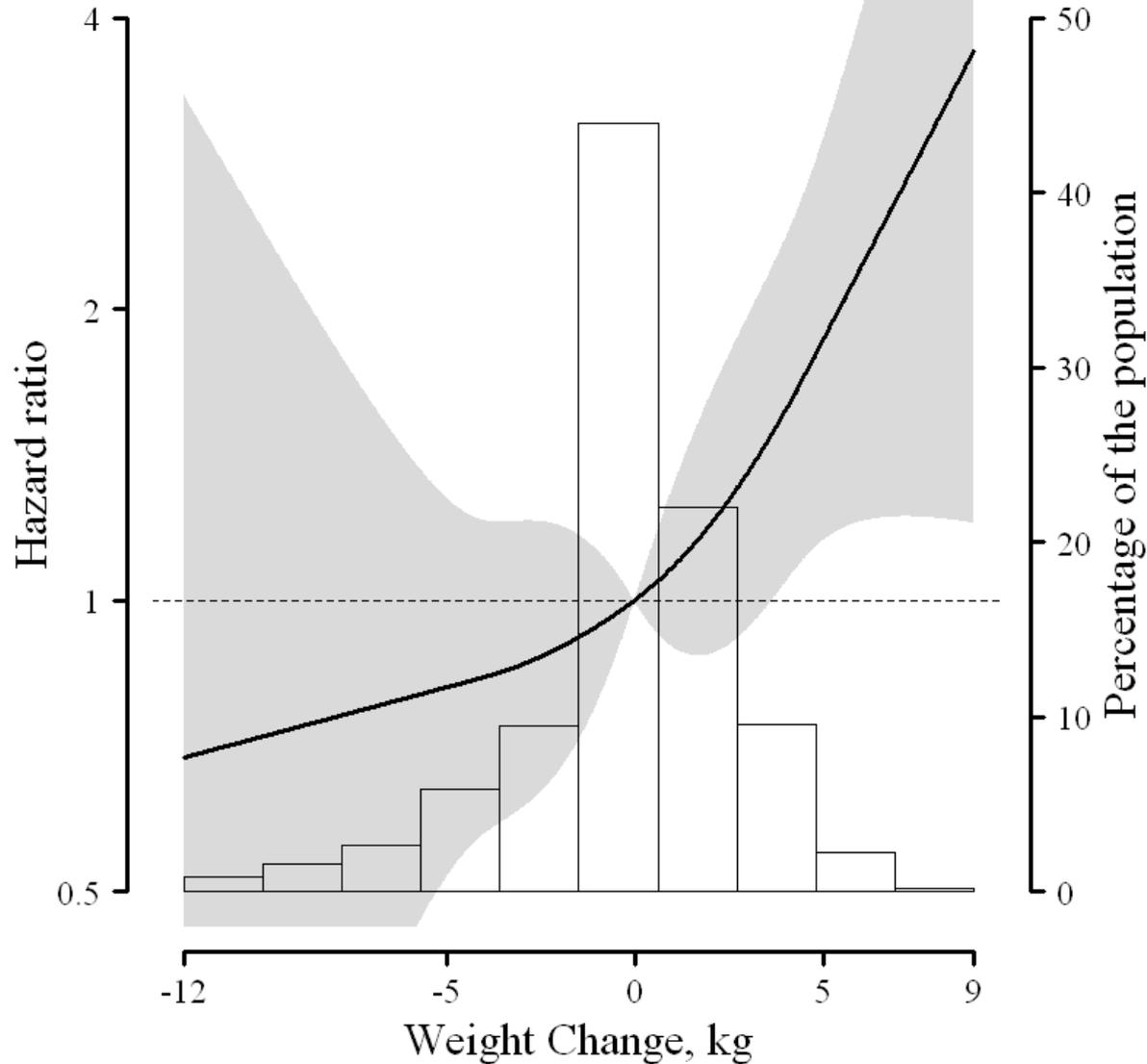
# Men who gain weight have a higher risk of prostate cancer recurrence after prostatectomy, JHH



**Weight change from 5 years before to 1 year after surgery**

Adjusted for weight 5 years before surgery, height, physical activity 1 year after surgery, age, race/ethnicity, family history, year of surgery, **stage, grade, and smoking status.**

# Men who gain weight have a higher risk of recurrence after prostatectomy, JHH



# Summary

- Evidence building that obesity/weight gain is a risk factor for poor outcome in men diagnosed with prostate cancer
  - Opposite may be true (weight loss), but much more work is needed
- Many knowledge gaps
- Many methodologic issues that need to be addressed
- Bottom line: May be an important modifiable risk factor for poor outcome in men with prostate cancer.