



# UNDERSTANDING EPIDEMIOLOGICAL STUDIES

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# Study design in epidemiological research: Summary

- Observational studies
  - Descriptive or case-series
  - Case-control studies (retrospective)
  - Cross-sectional studies, surveys (prevalence)
  - Cohort studies (prospective)
  - Historical cohort studies
- Experimental studies
  - Controlled trials
  - Studies with no controls



# Case series

- Descriptive account of an interesting characteristic
  - In one patient
  - In a small group of patients
- Usually involves patients seen over a short period of time
- Does not involve controls
- No research hypothesis
- Leads to formulation of hypotheses, other types of studies

# Proliferative Glomerulonephritis with Monoclonal IgG Deposits

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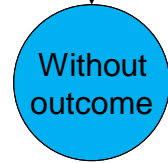
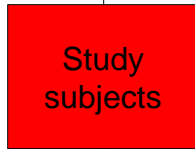
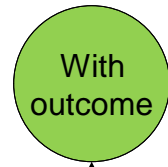
## ABSTRACT

Dysproteinemias that result in monoclonal glomerular deposits of IgG are relatively uncommon. Here, we report the largest series of proliferative glomerulonephritis with monoclonal IgG deposits, a form of renal involvement by monoclonal gammopathy that mimics immune-complex glomerulonephritis. We retrospectively identified 37 patients, most of whom were white (81%), female (62%), or older than 50 yr (65%). At presentation, 49% had nephrotic syndrome, 68% had renal insufficiency, and 77% had hematuria. In 30% of the patients, we identified a monoclonal serum protein with the same heavy- and light-chain isotypes as the glomerular deposits (mostly IgG1 or IgG2), but only one patient had myeloma. Histologic patterns were predominantly membranoproliferative (57%) or endocapillary proliferative (35%) with membranous features. Electron microscopy revealed granular, nonorganized deposits, and immunofluorescence demonstrated glomerular deposits that stained for a single light-chain isotype and a single heavy-chain subtype, most commonly IgG3 $\kappa$  (53%). During an average of 30.3 mo of follow-up for 32 patients with available data, 38% had complete or partial recovery, 38% had persistent renal dysfunction, and 22% progressed to ESRD. Correlates of ESRD on univariate analysis were higher creatinine at biopsy, percentage of glomerulosclerosis, and degree of interstitial fibrosis but not immunomodulatory treatment or presence of a monoclonal spike. On multivariate analysis, higher percentage of glomerulosclerosis was the only independent predictor of ESRD. Only one patient lacking a monoclonal spike at presentation subsequently developed a monoclonal spike and no patient with a monoclonal spike at presentation subsequently developed a hematologic malignancy. We conclude that proliferative glomerulonephritis with monoclonal IgG deposits does not seem to be a precursor of myeloma in the vast majority of patients.



# Cross sectional studies

- Analyze data collected at a single point in time
- Provide information on status quo (e.g. prevalence of a condition, or disease characteristics)



Study start

# Association of Serum Phosphorus Level With Anemia in Kidney Transplant Recipients

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**Background.** Anemia and mineral and bone disorders (MBD) are both important and common complications in kidney transplant recipients. Studies in patients with chronic kidney disease indicated a possible independent association of higher serum phosphorus with anemia, but similar associations have not been examined in kidney transplant recipients. We hypothesized that higher serum phosphorus is associated with anemia independent of other components of MBD.

**Methods.** We examined the association of serum phosphorus with hemoglobin level and the prevalence of anemia in a prevalent cohort of 992 kidney transplant recipients in a single outpatient transplant center. Associations were examined in linear and logistic regression models with adjustment for demographic and comorbid conditions for various known risk factors of anemia, including measures of iron deficiency, inflammation, and components of MBD including serum levels of 25(OH) vitamin D, parathyroid hormone, and fibroblast growth factor 23.

**Results.** In multivariable adjusted regression models, a 1 standard deviation (0.8 mg/dL) higher serum phosphorus level was associated with 0.26 g/dL lower blood hemoglobin concentration (95% confidence intervals  $-0.36$  to  $-0.15$ ,  $P < 0.001$ ) and with an odds ratio for anemia of 1.77 (95% confidence intervals 1.33–2.37,  $P < 0.001$ ). These associations were consistent across the entire spectrum of the physiologic serum phosphorus concentration and were more accentuated in patients with lower estimated glomerular filtration rate.

**Conclusions.** Higher serum phosphorus is independently associated with anemia in kidney transplant recipients.

**Keywords:** Serum phosphorus, Hemoglobin, Anemia, Kidney transplant.

(*Transplantation* 2011;91: 875–882)



# Cross sectional studies

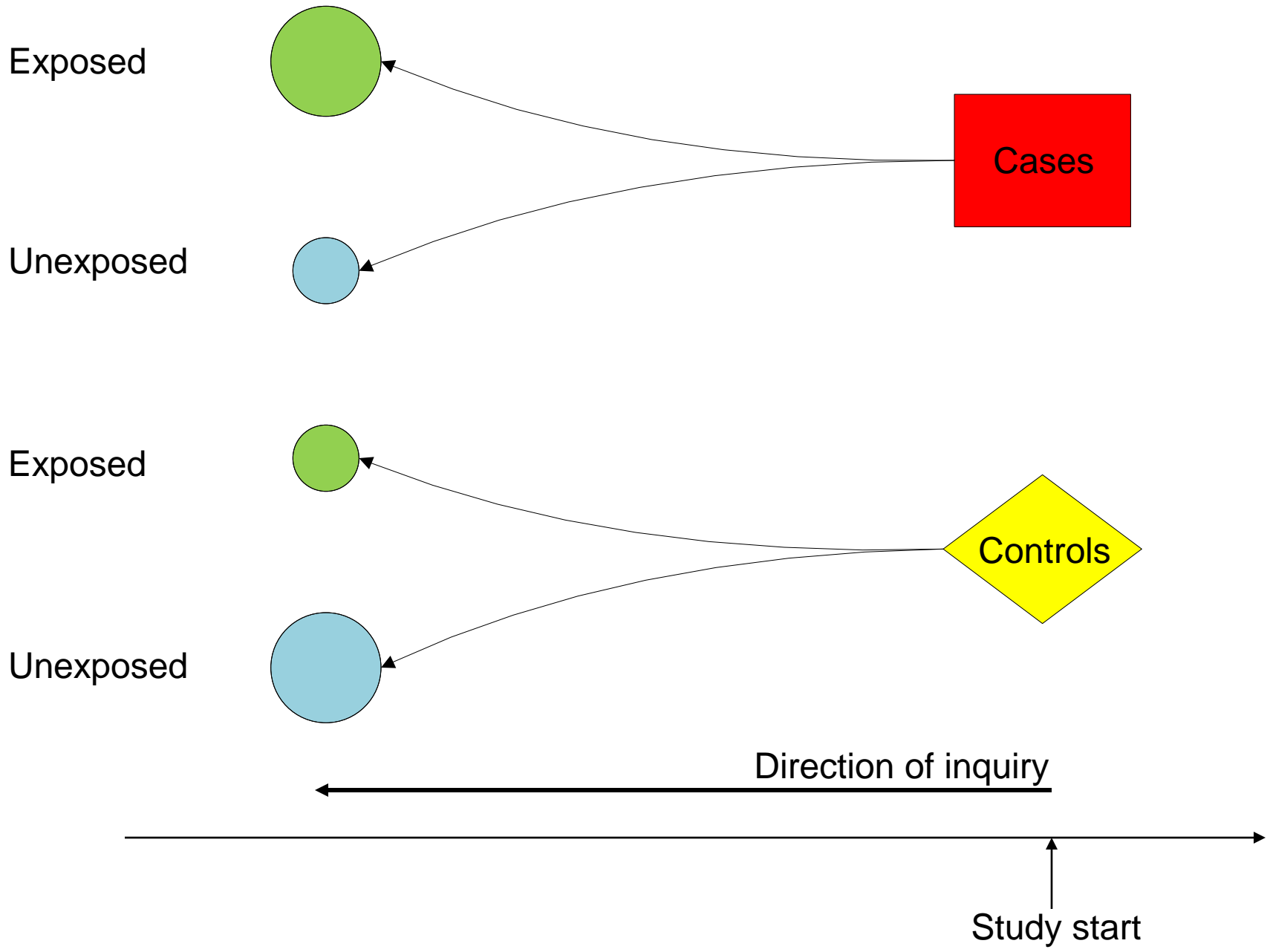
- Cross sectional advantages
  - Quick to complete, cheap
- Cross sectional disadvantages
  - Provides a snapshot in time, no information on disease process
    - Cannot examine outcomes
    - May lead to biased conclusions about disease progression (e.g. does DBP change with age?)





# Case control studies

- Longitudinal, retrospective design
- Starts with the outcome
  - Cases: those with the outcome
  - Controls: those without the outcome
- Looks back in time to determine exposure
- Differentiation between case control and case series not always easy
  - Presence of hypothesis



# Association of Trypanolytic ApoL1 Variants with Kidney Disease in African Americans

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African Americans have higher rates of kidney disease than European Americans. Here, we show that, in African Americans, focal segmental glomerulosclerosis (FSGS) and hypertension-attributed end-stage kidney disease (H-ESKD) are associated with two independent sequence variants in the *APOL1* gene on chromosome 22 {FSGS odds ratio = 10.5 [95% confidence interval (CI) 6.0 to 18.4]; H-ESKD odds ratio = 7.3 (95% CI 5.6 to 9.5)}. The two *APOL1* variants are common in African chromosomes but absent from European chromosomes, and both reside within haplotypes that harbor signatures of positive selection. ApoL1 (apolipoprotein L-1) is a serum factor that lyses trypanosomes. In vitro assays revealed that only the kidney disease–associated ApoL1 variants lysed *Trypanosoma brucei rhodesiense*. We speculate that evolution of a critical survival factor in Africa may have contributed to the high rates of renal disease in African Americans.

# Case-control studies

## ■ Case-control advantages

- Shorter
- Cheaper
- Useful to study rare diseases or diseases that take a long time to manifest, or to explore preliminary hypotheses

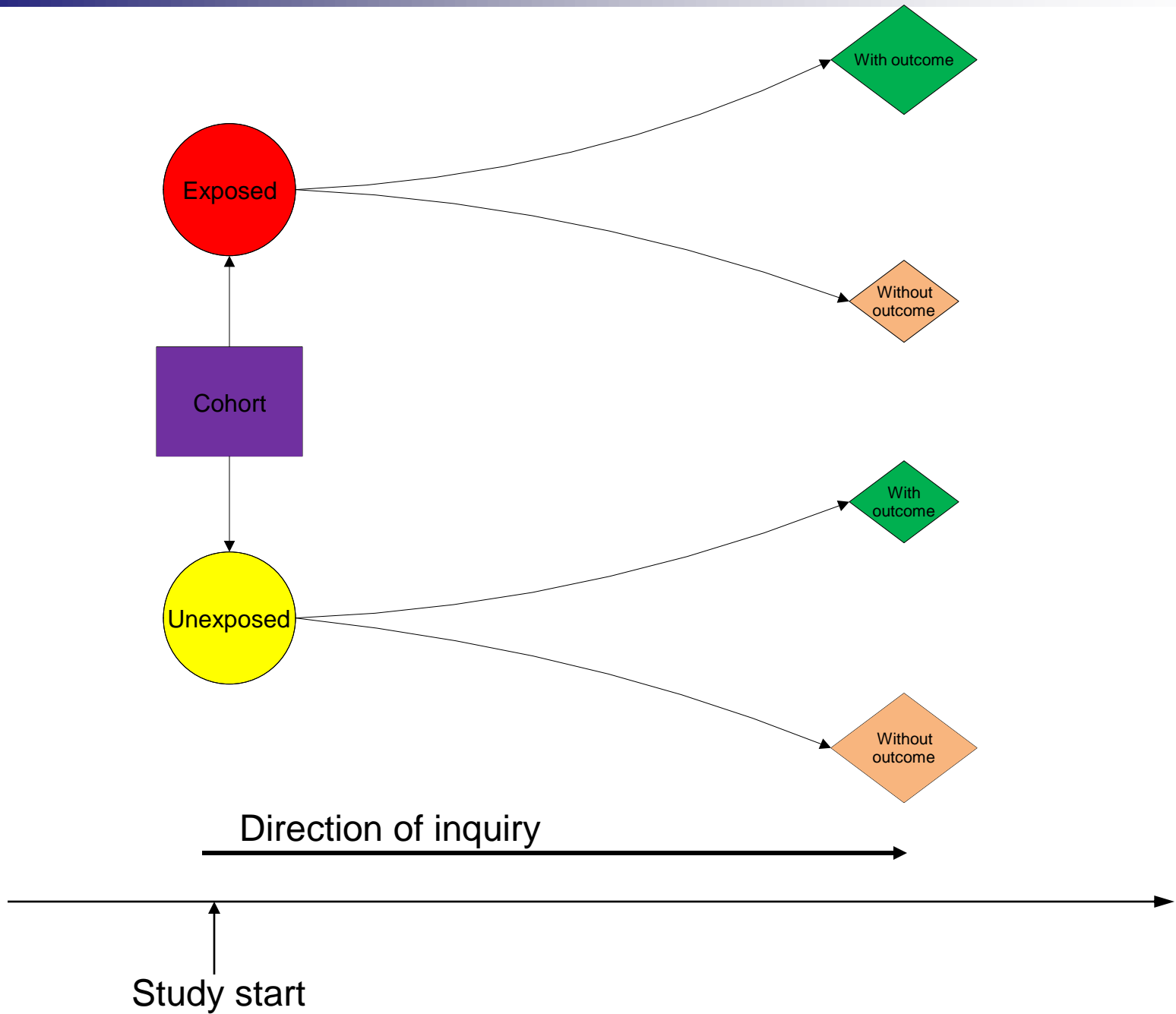
## ■ Case-control disadvantages

- Difficult to control for bias
- May depend entirely on quality of existing records
- Can be difficult to designate appropriate control group



# Cohort studies

- Cohort: a group of people who have something in common and who remain part of a group over an extended period of time
  - In medicine this usually means a characteristic that is known to be a risk factor (e.g. CKD)
- Outcomes determined after follow-up: longitudinal, prospective studies



# Body Mass Index, Waist Circumference and Mortality in Kidney Transplant Recipients

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**Key words:** body mass index, kidney transplant, mortality, waist circumference

**Abbreviations:** BMI, body mass index; CKD, chronic kidney disease; CI, confidence interval; CRP, C-reactive protein; DGF, delayed graft function; ESRD, end stage renal disease; SBP, systolic blood pressure.

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## Introduction

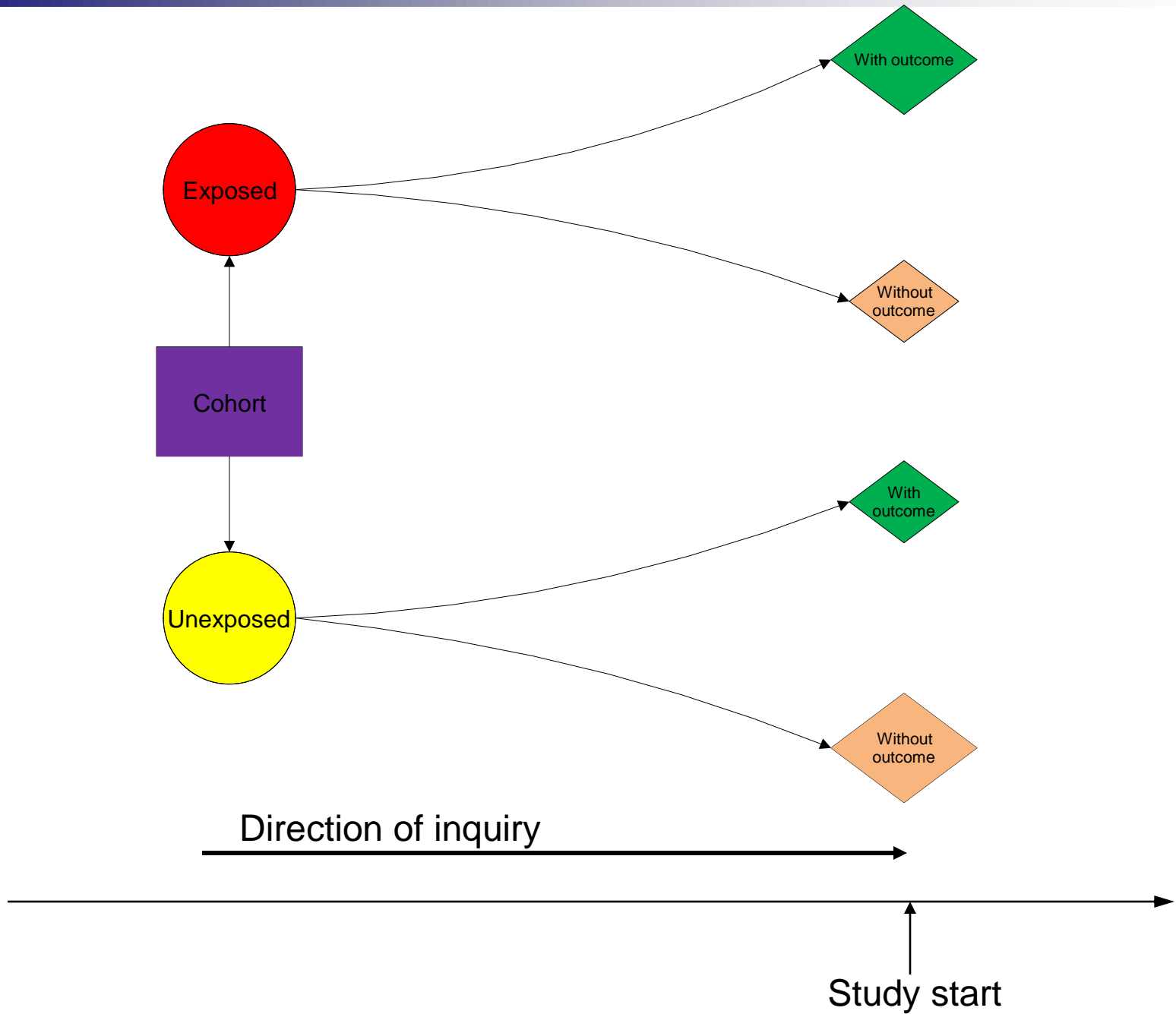
An obesity epidemic in both developed and developing countries (1) has been implicated as a cause of various comorbidities including diabetes mellitus, atherosclerotic cardiovascular disease, cancer and chronic kidney disease (CKD) (2–5), and has been linked to higher mortality in the general population (6). Yet obesity, usually defined as a



# Historical cohort studies

- Same as cohort studies, but uses information that was collected in the past
  - A.K.A. “retrospective cohort study”
- Valid if data is complete and subjects’ status is ascertained





# Paradoxical Association Between Body Mass Index and Mortality in Men With CKD Not Yet on Dialysis

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and Kamyar Kalantar-Zadeh, MD, PhD, MPH<sup>4,5</sup>*

**Background:** Low body mass index (BMI) is associated with greater mortality in patients on dialysis therapy. This relationship is less well characterized in patients with chronic kidney disease (CKD) who are not yet on dialysis therapy.

**Study Design:** Historic prospective cohort.

**Setting & Participants:** 521 male US veterans with CKD (age,  $68.8 \pm 10.4$  years; 21.3% black; estimated glomerular filtration rate,  $37.5 \pm 16.8$  mL/min/1.73 m<sup>2</sup> [ $0.62 \pm 0.28$  mL/s/1.73 m<sup>2</sup>]) at a single medical center.

**Predictor:** BMI.

**Outcomes & Measurements:** Associations with all-cause mortality were explored in fixed-covariate and time-dependent Cox models and sequentially adjusted for demographic characteristics (age and race), case-mix (comorbidity index, smoking, blood pressure, estimated glomerular filtration rate, and medication use), and surrogates of malnutrition and inflammation (serum albumin, cholesterol, and bicarbonate levels; white blood cell count; percentage of lymphocytes; and hemoglobin level).

**Results:** Patients were followed up for up to 5.5 years, and the mortality rate was 128.3 deaths/1,000 patient-years (95% confidence interval [CI], 110.5 to 149.0). Higher BMI was associated with lower mortality in the fixed-covariate Cox models, including the fully adjusted model (adjusted hazard ratios for mortality in the group with BMI in 10th to 50th, 50th to 90th, and >90th versus <10th percentiles, 0.75 [95% CI, 0.46 to 1.22], 0.56 [95% CI, 0.33 to 0.94], and 0.39 [95% CI, 0.17 to 0.87];  $P_{\text{trend}} = 0.005$ ). Associations were similar in a time-dependent Cox model ( $P_{\text{trend}} = 0.008$  in the fully adjusted model).

**Limitations:** Results may not be generalizable.

**Conclusions:** Lower BMI is associated with greater mortality in patients with CKD not yet on dialysis therapy. Adjustment for case-mix and surrogate markers of malnutrition and inflammation attenuated, but did not reverse, this relationship.

# Cohort studies

## ■ Cohort advantages

- Better to control sources of bias (prospective cohort studies)
- Ideal for conditions that have high mortality or take a short time to develop

## ■ Cohort disadvantages

- May take a long time (cost, attrition)
- Difficult if condition is rare (large number of subjects required)



# Case-control vs. Cohort

- Can combine the two: case-cohort, or nested case-control study
  - Identifies cases and controls within an existing cohort

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Fibroblast Growth Factor 23 and Mortality among Patients Undergoing Hemodialysis

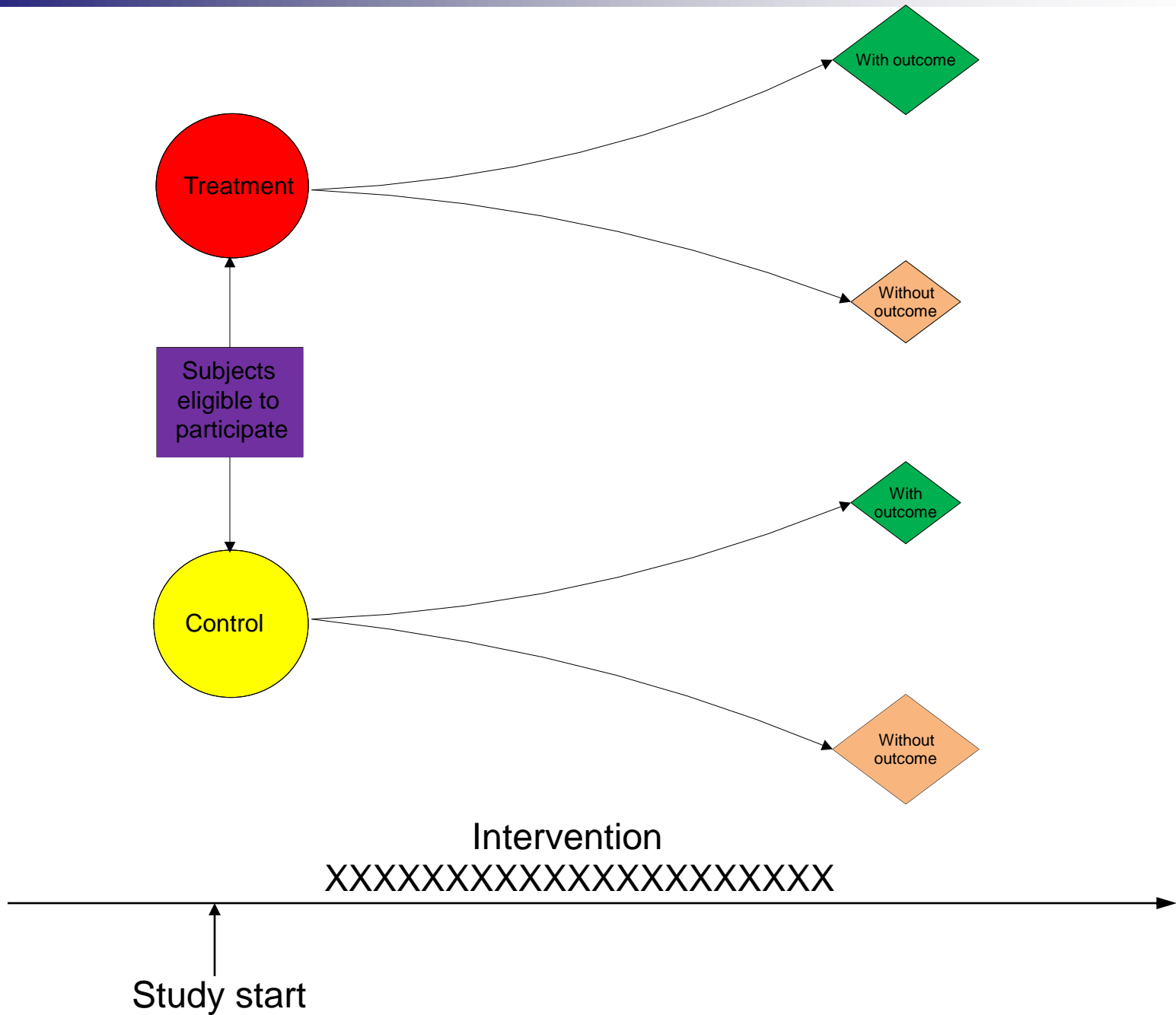
Orlando M. Gutiérrez, M.D., M.M.Sc., Michael Mannstadt, M.D.,  
Tamara Isakova, M.D., Jose Alejandro Rauh-Hain, M.D., Hector Tamez, M.D.,  
Anand Shah, M.D., Kelsey Smith, B.A., Hang Lee, Ph.D.,  
Ravi Thadhani, M.D., M.P.H., Harald Jüppner, M.D., and Myles Wolf, M.D., M.M.Sc.

# Experimental studies, a.k.a. clinical trials

- Controlled: intervention is compared to another intervention or to a placebo
- Uncontrolled: describe investigators' experience with an intervention, without a comparison group
  - Strictly speaking these are not clinical trials

# Controlled clinical trials

- Two groups that are identical and are treated the same except for the intervention of interest
  - Concurrent controls
  - Blinding (double blind, single blind)
    - Reduces the chances that the patient or the investigator “see” what they expect to see
  - Randomization procedure
    - Reduces the chances for bias
    - Best evidence for causal inference





# Paricalcitol Versus Ergocalciferol for Secondary Hyperparathyroidism in CKD Stages 3 and 4: A Randomized Controlled Trial

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Dennis L. Andress, MD,<sup>4</sup> Kamyar Kalantar-Zadeh, MD, PhD,<sup>5,6</sup> and  
Shahram Ahmadzadeh, MD<sup>1</sup>

**Background:** The efficacy of 25-hydroxyvitamin D (25[OH]D) supplementation versus vitamin D receptor activators for the treatment of secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) stages 3/4 and vitamin D deficiency is unclear.

**Study Design:** Randomized controlled trial.

**Setting & Participants:** 80 patients with CKD stages 3/4, 25(OH)D level <30 ng/mL, and SHPT in a single medical center.

**Intervention:** Ergocalciferol, 50,000 units, titrated to achieve serum levels  $\geq 30$  ng/mL versus paricalcitol, 1 or 2  $\mu\text{g}/\text{d}$ , for 16 weeks.

**Outcomes:** The occurrence of 2 consecutive parathyroid hormone (PTH) levels decreased by at least 30% from baseline. All analyses were intention to treat.

**Results:** Baseline characteristics in the 2 groups were similar. 21 patients (53%) on paricalcitol and 7 patients (18%) on ergocalciferol treatment achieved the primary outcome measure ( $P = 0.002$ ). After 16 weeks, PTH levels did not decrease significantly in patients receiving ergocalciferol, but were decreased significantly in those treated with paricalcitol (mean estimate of between-group difference over 16 weeks of therapy, 43.9 pg/mL; 95% CI, 11.2-76.6;  $P = 0.009$ ). Serum 25(OH)D levels increased significantly after 16 weeks in only the ergocalciferol group, but not the paricalcitol group (mean estimate of between-group difference over 16 weeks of therapy, 7.08 ng/mL; 95% CI, 4.32-9.85;  $P < 0.001$ ). Episodes of hyperphosphatemia and hypercalcemia were not significantly different between the 2 groups.

**Limitations:** Lack of blinding and use of surrogate end points.

**Conclusions:** Paricalcitol is more effective than ergocalciferol at decreasing PTH levels in patients with CKD stages 3 or 4 with vitamin D deficiency and SHPT.

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**INDEX WORDS:** Parathyroid hormone; vitamin D; ergocalciferol; paricalcitol; clinical trial.



# Trials with self-controls

- Patients are used as their own controls
  - Smaller numbers of patients needed
- Vulnerable to the Hawthorne effect
  - Patients change their behavior and improve due to their participation in the study, and not because of the intervention
- Patients may change over time
- Prone to bias by carry-over effect
  - Variant: cross-over study
- Less well suited to examine adverse events



# Trials with external controls

- Controls can be patients in another study of the same or alternative intervention, or patients treated in the past in another manner (historical controls)
- Can be used for conditions without a cure (AIDS, some malignancies)
- Often used to explore a new/preliminary hypothesis
- Disadvantage: other factors besides the intervention may have changed
  - Bias in patient selection



# RCTs

- RCT advantages

- Best to use if goal is to determine the efficacy and safety of a treatment/procedure
  - least number of biases
  - greatest proof of causality

# RCTs

- RCT disadvantages

- \$\$\$\$\$\$\$\$\$

- Duration

- Hard to examine “established” treatments

- Difficult to obtain funding, IRB approval

- External validity

- Inappropriate design, study conduct

- Unsuccessful randomization

- Incomplete follow-up, drop-outs: decreased power

- Crossing over: as treated vs. intention-to-treat



- Questions