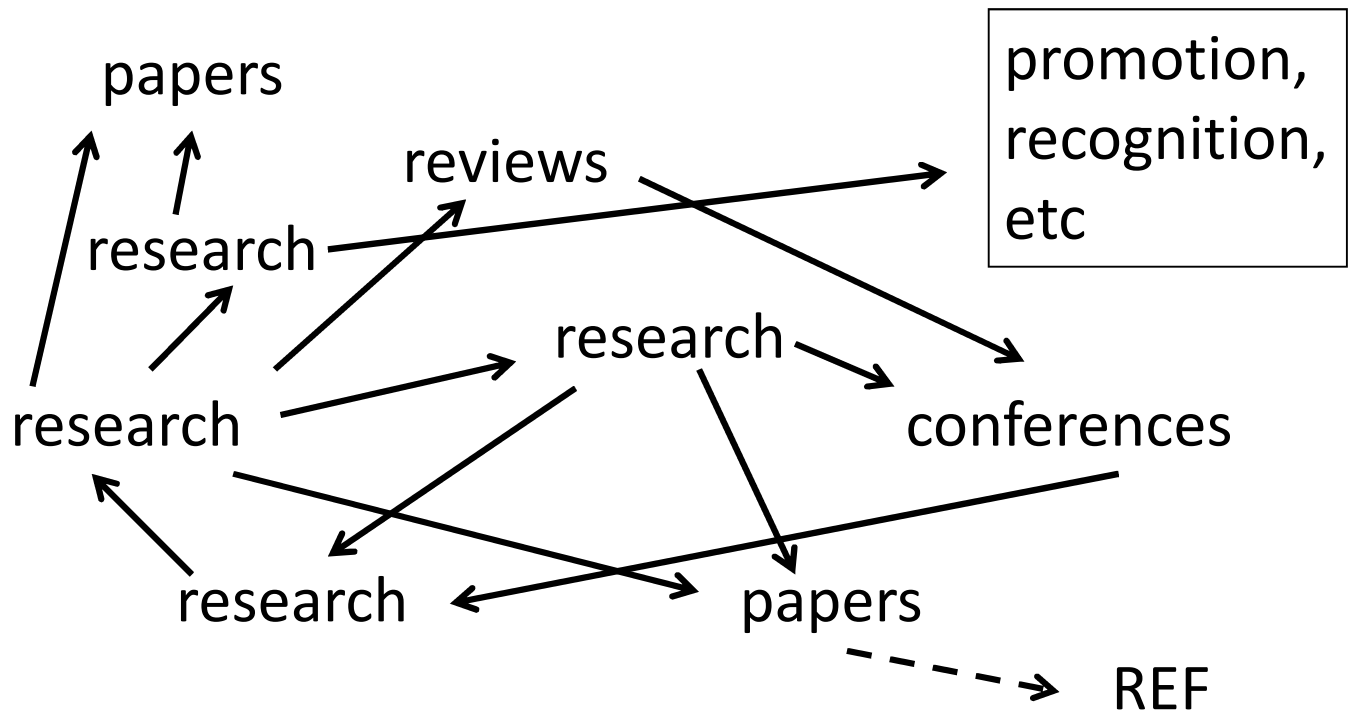
How to get NIHR grant funding

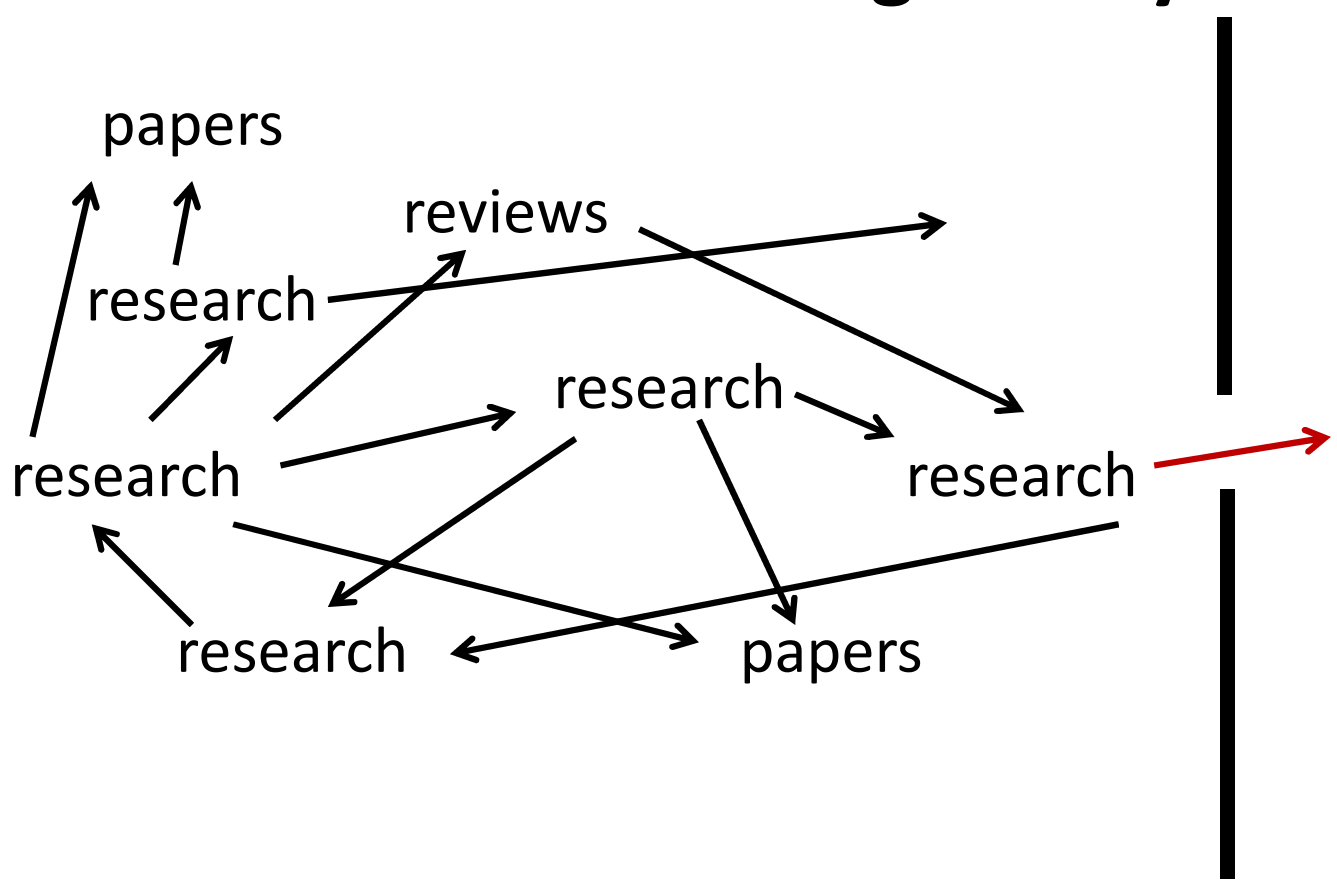
David Armstrong

Director, NIHR Research for Patient Benefit programme

Research



The NIHR research gateway



NIHR research

research

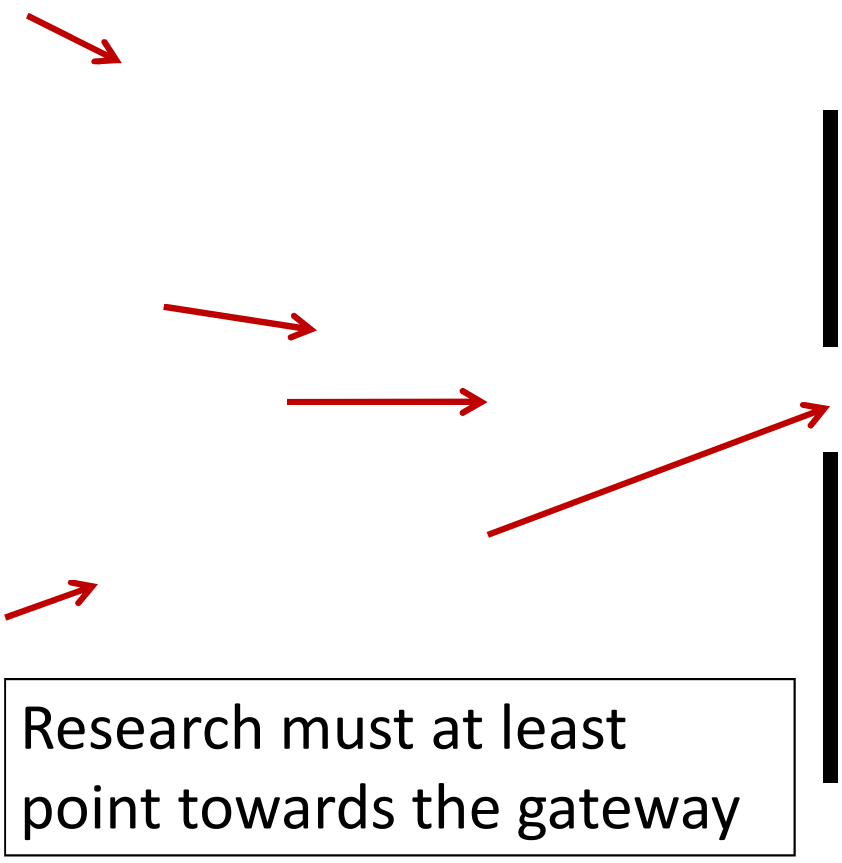
<u>Research synthesis and interpretation</u>

- Systematic reviews
- NICE

<u>'Customers'</u>

– Clinicians
– Patients
– Commissioners

NIHR research



Research must at least point towards the gateway

Research synthesis and interpretation

NIHR research

Which research will clearly go through the gateway?

Clinical trials

Research synthesis and interpretation

NIHR clinical trials

- NIHR is the major public funder of clinical trials
- Trials provide best unbiased estimate of the effectiveness of any intervention
- These results can be fed into a systematic review/meta-analysis
- Systematic reviews form the basis of NICE guidance
- NICE guidance can influence patients, clinicians and commissioners

Which trials won't go through the gateway?

1. The wrong question?
2. The wrong choice of primary endpoint?
3. The wrong numbers?
4. Trial is not feasible?

Trial design: Avoiding the wrong question?

- Current clinical uncertainty?
- New intervention ('window of opportunity')?
- Not covered in systematic review (or clinical trials gateway)?

Trial design: Avoiding the wrong question?

Right comparator?

- Drug industry uses placebo to show effectiveness for licensing purposes
- NIHR trials need to compare intervention with commonly used existing treatments (TAU - 'treatment as usual')
- Need to justify/explain reason for choice

Trial design: Choosing the right primary endpoint

- How effective is this therapy in terms of …?
- Best is patient/clinically relevant endpoint: mortality, pain, quality of life, ADLs, etc
- Less helpful are 'surrogate' endpoints such as cardiac ejection fraction, FEV, CD4 count, etc

  unless clear 'translation':
  - less smoking – less COPD – lower mortality
  - lower BP – fewer strokes

Trial design: Choosing the right primary endpoint

- Surrogate endpoints sometimes justified: Eg cardiac ejection fraction in new treatment for heart failure
- Phase II trial: is treatment effective for surrogate endpoint?
- Then Phase III trial with clinical/patient relevant endpoints
- Will NIHR fund Phase II trials? Sometimes: seen as risky – needs a good case making

Trial design:
Are the numbers right?

- All trials must have a power calculation
- How many patients are needed to show that if, say, intervention provides a 20% improvement over control arm, that improvement will be identified
- So need to pre-specify ‘effect size’

Trial design:
Powering and effect size

Choosing an effect size for a trial:

- The smaller the effect size the bigger (and more expensive) the trial
- Choosing too big an effect size may miss an important clinical effect

How common are large effect sizes?

Cochrane database:

228,220 trials, 85,000 trial syntheses

- First published and small trials tend to report bigger effect sizes
- 9% reported large effect sizes (OR>5) but for non-fatal outcomes; only one intervention for mortality (extracorporeal oxygenation for severe respiratory failure in newborns)

JAMA, October 24/31, 2012

Powering and effect size

Meta-analysis of primary prevention trials of statins

Outcome	No. trials	No. participants	No. Needed to Treat for 5y (95% CIs)
All cause mortality	13	24,408	138 (92-321)
Total CHD events	14	24, 217	88 (72-119)
Total stroke events	10	20,302	155 (106-309)

JAMA 2013

Powering and effect size

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JAMA 2013

Trial design: Powering and effect size

- How plausible is proposed effect size (is it too big?)
- Would a smaller effect size (which is likely to be missed) be clinically relevant?
- So is the trial the right size?

Trial design:
Is the trial feasible?

- In particular, will it recruit and retain sufficient patients?
- (most common reason for trials failing or needing additional time/money is recruitment)
- NIHR may be willing to fund a feasibility study

‘Proof of concept’ studies?

- Mostly too upstream for NIHR
- Though might be funded as part of bigger project
- Needs to have clear trajectory into likely patient benefit
- (animal work not funded)

Non-randomised evaluations

- May be funded: but need to argue that trial not possible (eg effect of long term lifestyle changes)
- But effect sizes tend to be unreliable and tend to be inflated

Risk factor research

- Aetiological research not suitable for NIHR funding
- But what if identifying a ‘modifiable’ risk factor?

Risk factor ‘association studies’

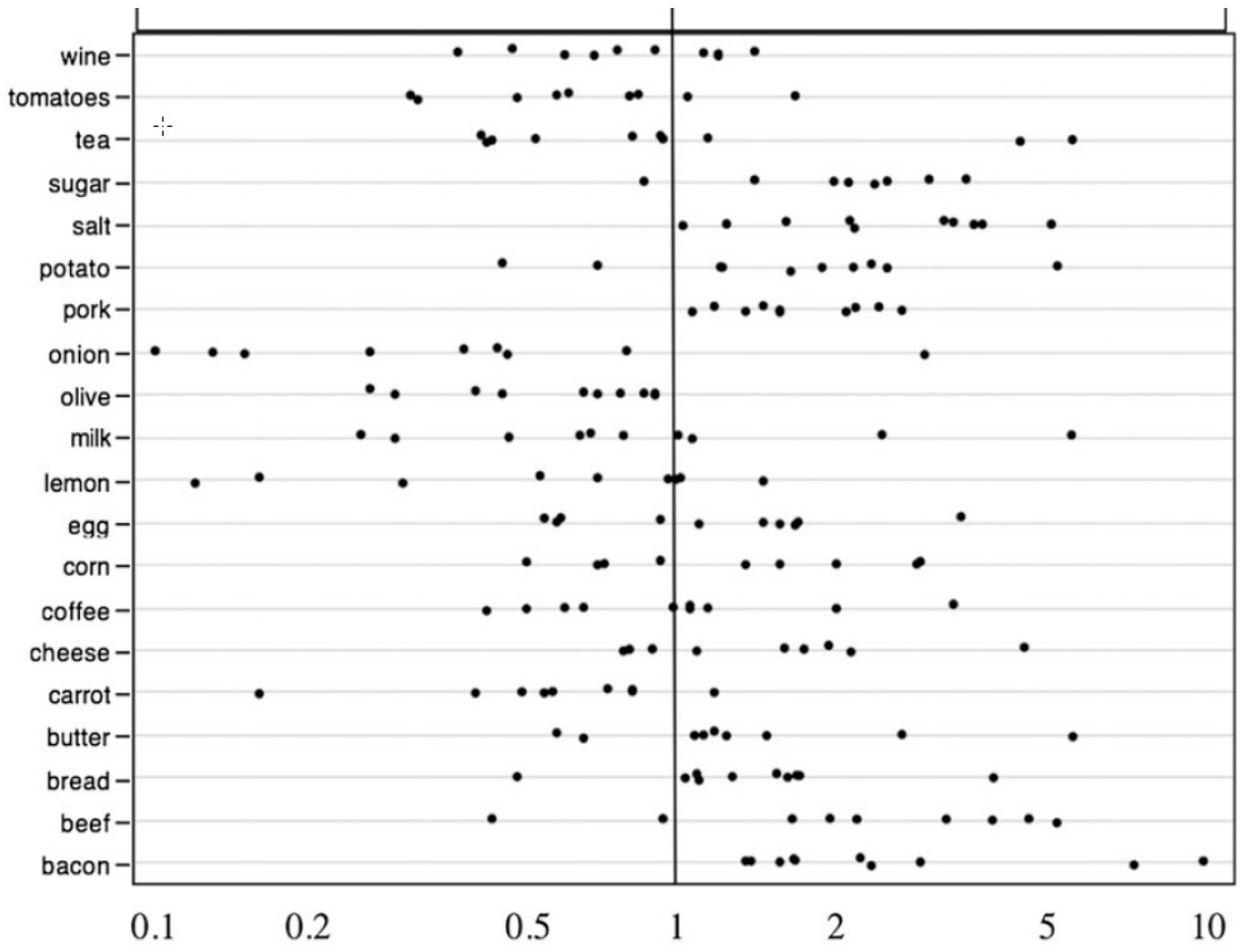
- Open a popular cookbook
- Randomly check 50 ingredients
- How many associated with significantly increased or significantly decreased cancer risk?
- 80% had papers reporting on their cancer risk
- (75% of the risk estimates had weak or no statistical significance)

AmJClNn 2012

Risk factor ‘association studies’

veal, salt, pepper spice, flour, egg, bread, pork, butter, tomato, lemon, duck, onion, celery, carrot, parsley, mace, sherry, olive, mushroom, tripe, milk, cheese, coffee, bacon, sugar, lobster, potato, beef, lamb, mustard, nuts, wine, peas, corn, cinnamon, cayenne, orange, tea, rum, raisin

Relative risks



Vitamin D

- In observational studies vit D levels associated with fractures, IHD, cerebrovascular disease and cancer

- Meta-analysis of trials – no value for vitamin D supplementation

Lancet Diabetes 2014

NIHR research

- Non-randomised evaluations struggle to get funded
- Risk factor identification (assuming modifiable) struggle to get funded

Diagnostic studies

- Much less common than evaluations of therapy
- But important – more are needed

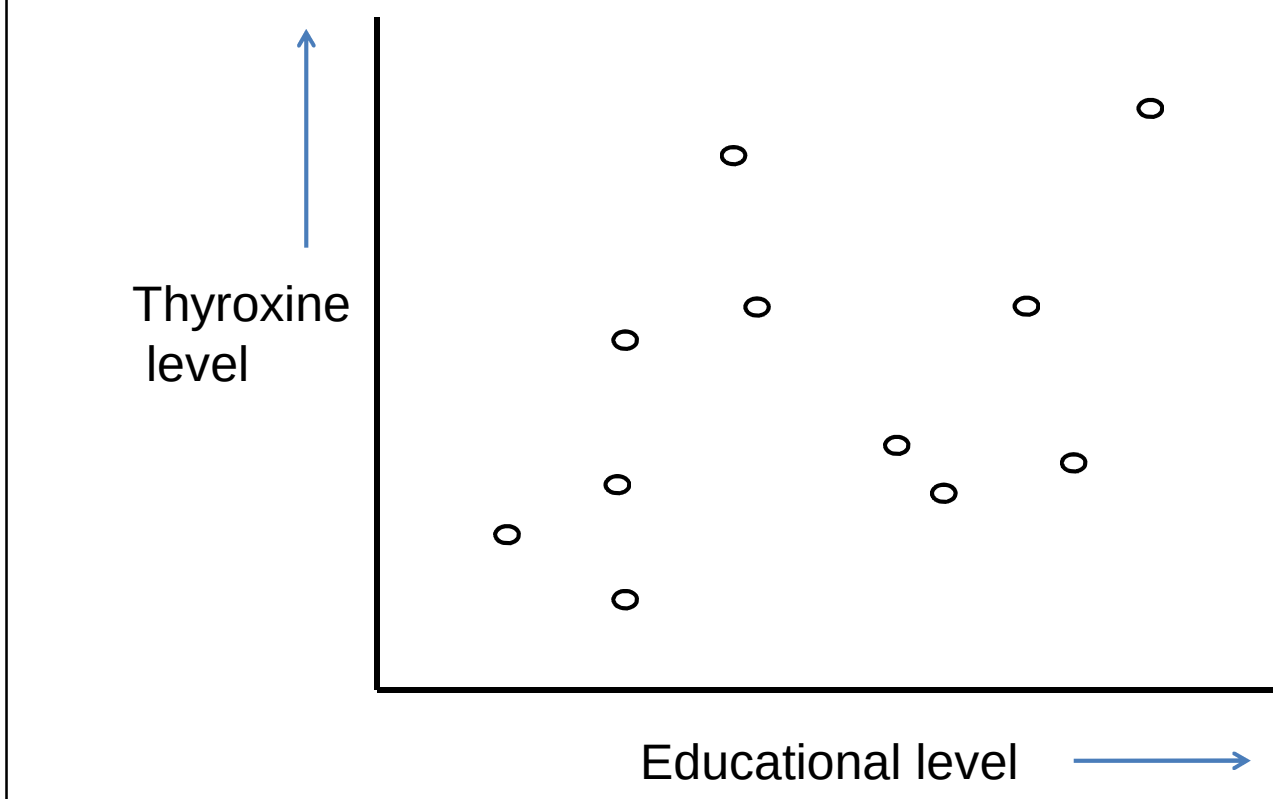
A recent NIHR application

- Was a baby's thyroxine level associated with their school educational achievement?

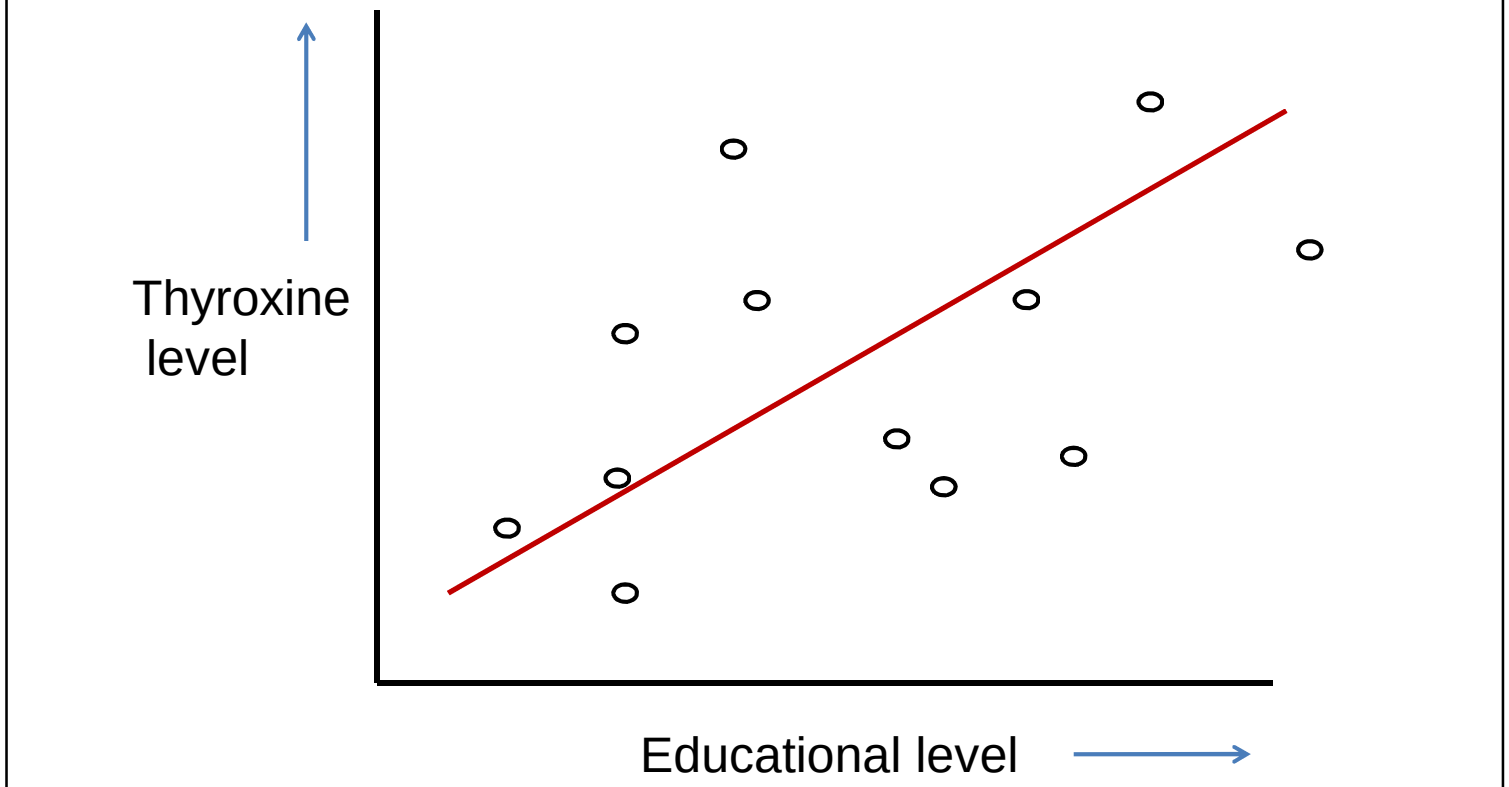
❑ Database of thyroxine levels at birth
❑ Database of starting school educational level

- Examine regression line to see level of association

A recent NIHR application



A recent NIHR application



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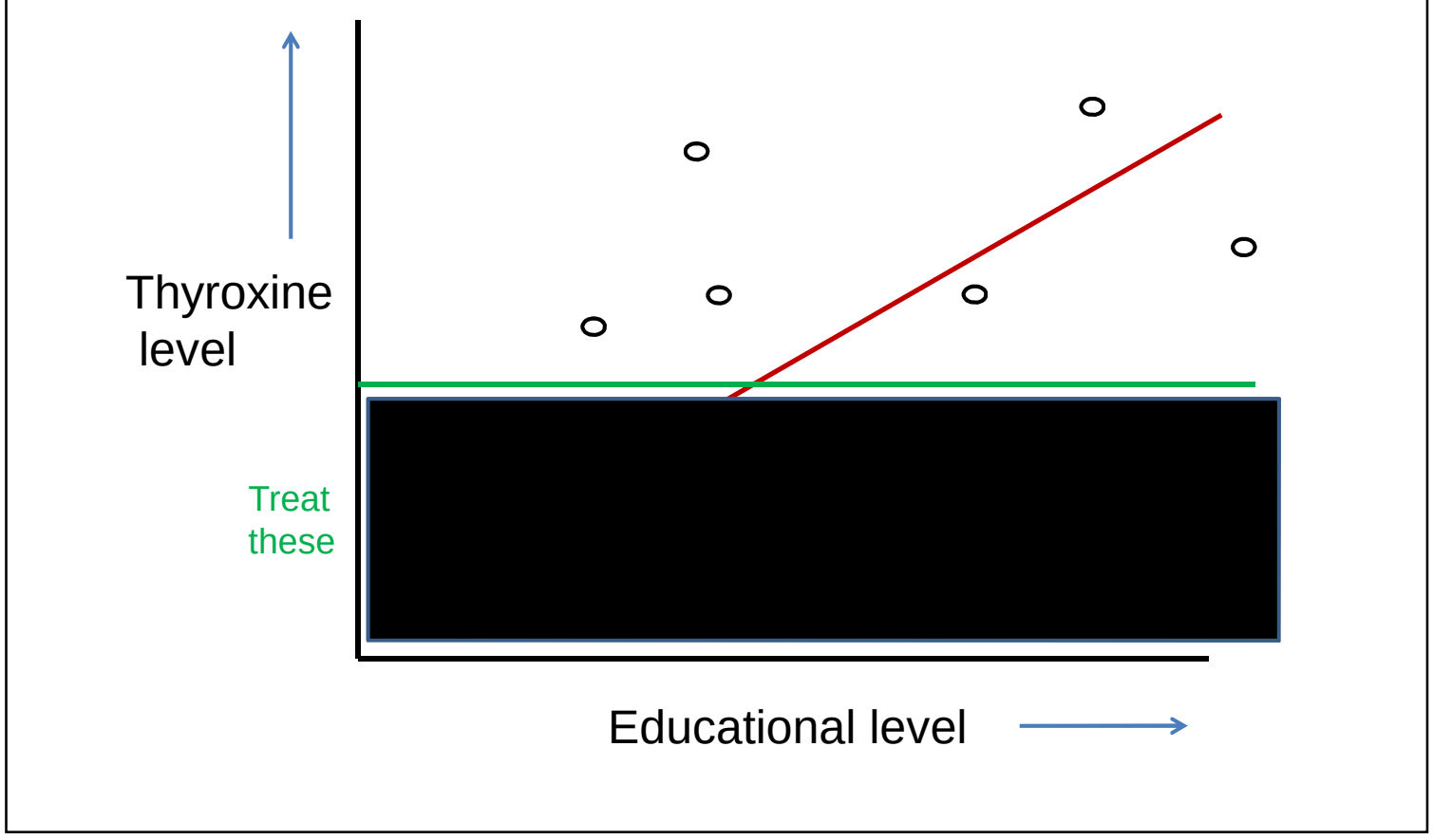

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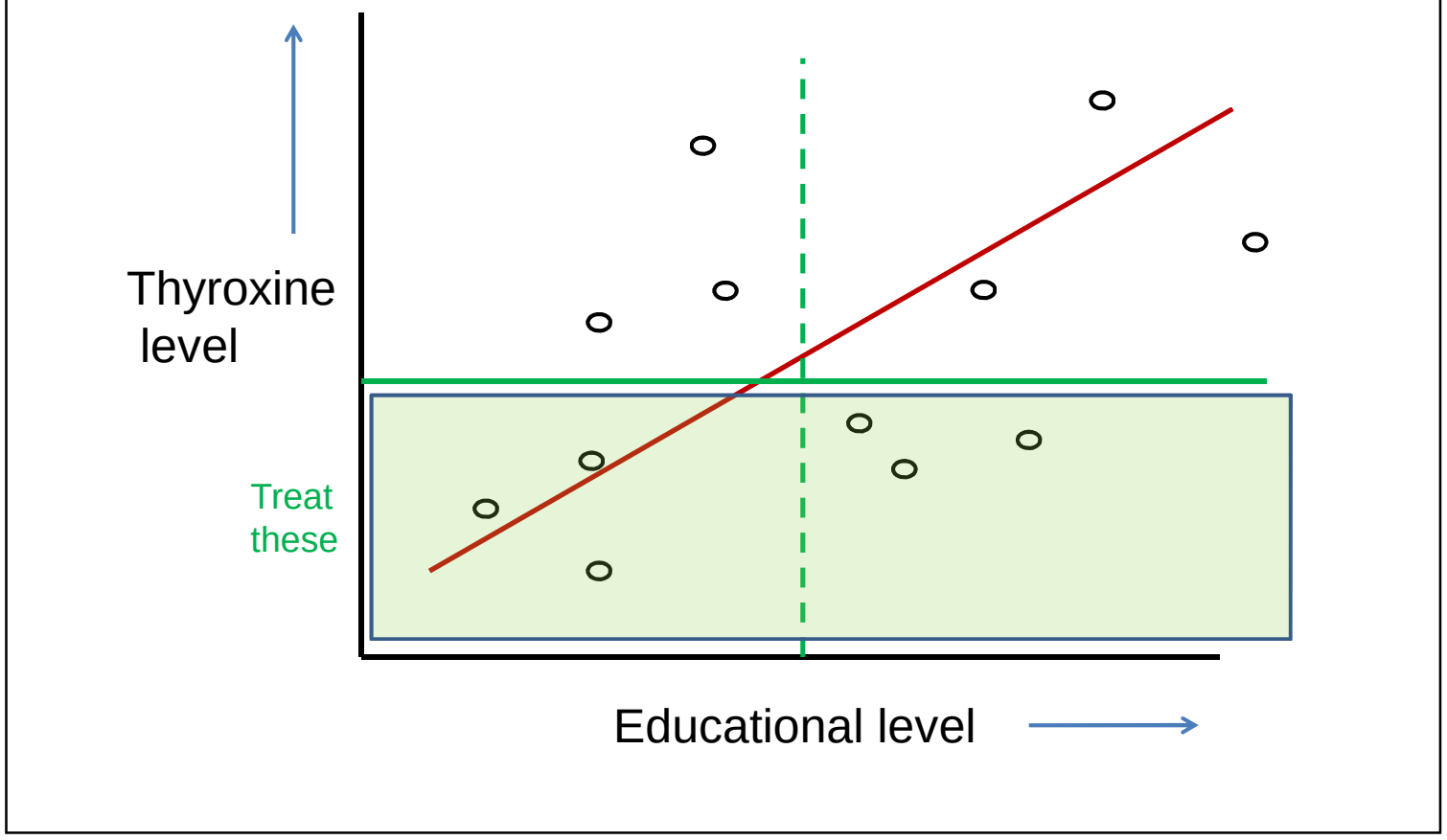

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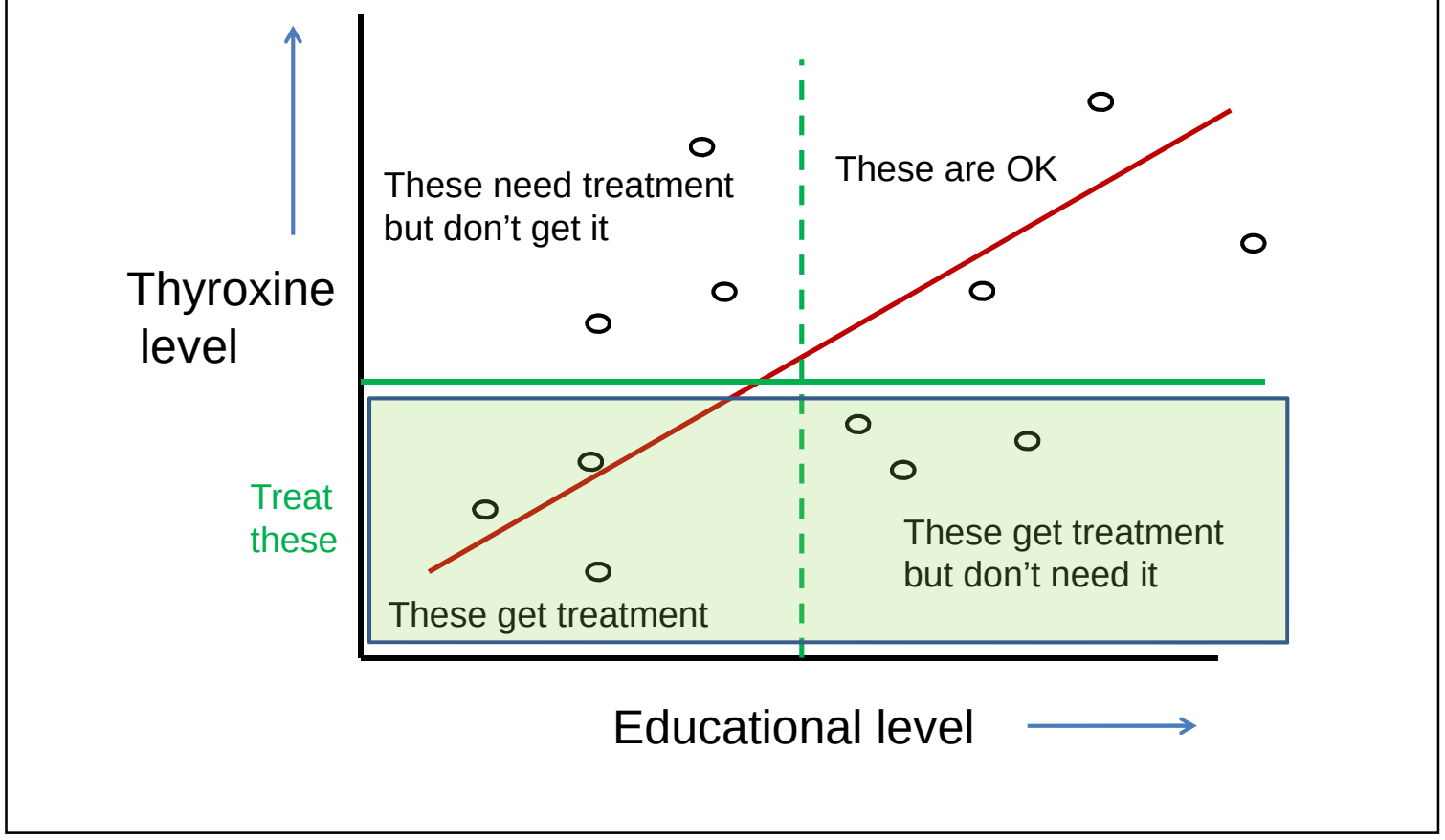

A recent NIHR application

- Was a baby's thyroxine level associated with their school educational achievement?
- The regression line does not help clinical decision-making/patient benefit
- To know whether thyroxine levels at birth can predict educational achievement we need to know the rate of false positives and false negatives …

A diagnostic accuracy study

	Educational need	No educational need
Test is positive	A True Positive	B False Positive
Test is negative	C False Negative	D True Negative

A diagnostic accuracy study

	Patient with the disease	Patient without the disease
Test is positive	A True Positive	B False Positive
Test is negative	C False Negative	D True Negative

Sensitivity & Specificity

	Disease +	Disease -	Total
Test +	25	2	27
Test -	5	68	73
Total	30	70	100

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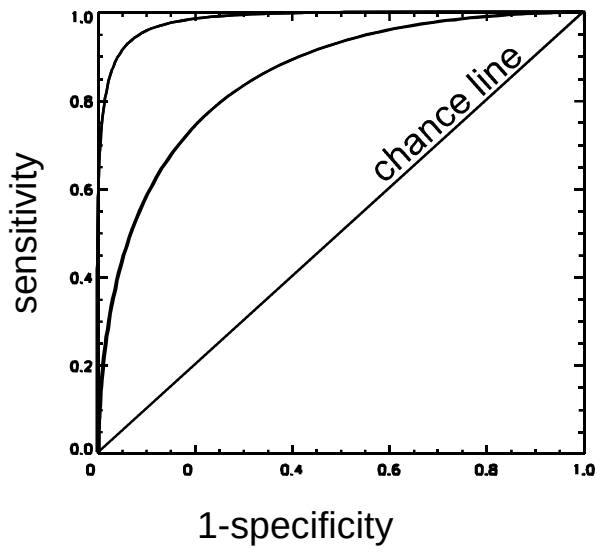
25/30 sensitivity	**68/70** specificity

Receiver Operator Characteristic (ROC) curve



Measure area under the curve (AUC)

Diagnostic accuracy studies

- Is the study trying to predict something?
  [diagnosis, prognosis, screening]

- It needs a gold standard/reference test
- It needs to estimate sensitivity/specificity (or positive/negative predictive value)
- It needs to be powered on these parameters

Diagnostic utility studies

- Is the study trying to test whether a diagnosis, followed by treatment, achieves patient benefit?

This needs a trial (the diagnosis is an 'intervention'):

- Randomise patients to two diagnostic processes, then treat
- Compare endpoints

Biomarkers

- "At least 10 cardiovascular biomarkers that can be measured in blood have accrued more than 6,000 published related papers each. A systematic evaluation of the evidence suggests that they have limited or no predictive ability for cardiovascular disease…" Circ Res 2012

- "Almost all articles on cancer prognostic markers report statistically significant results" Eur J Cancer 2007

- "No new major cancer biomarkers have been approved for clinical use for at least 25 years" JNCI 2010

Biomarkers

- Most biomarkers are a very long way from diagnostic or prognostic benefit

- NIHR likely to be cautious about funding

NIHR funding streams

- Health Technology Assessment
- Public Health Research
- Health Services and Delivery Research
- Efficacy and Mechanism Evaluation (funded by MRC)
- Programme Grants for Applied Research
- Research for Patient Benefit
- Invention for Innovation

NIHR funding schemes

- **Health Technology Assessment**
- **Public Health Research**
- **Health Services and Delivery Research**
- **Efficacy and Mechanism Evaluation (funded by MRC)**

Response-mode
and commissioned

- Programme Grants for Applied Research
- Research for Patient Benefit

Response-mode

- Invention for Innovation

Primary Research - Two Stage (outline to full proposal)

Deadline for applications - 8 May 2014, by 1pm

Topic	Deadline	Commissioning brief	Guidance notes	Apply
13/150 Self-sampling for sexually transmitted infections in men who have sex with men	8 May 2014, by 1pm	Access commissioning brief (pdf, 122.39 KB)	Access guidance notes (pdf, 320.28 KB)	Apply
13/151 Interventions for small bowel Crohn's disease	8 May 2014, by 1pm	Access commissioning brief (pdf, 122.24 KB)	Access guidance notes (pdf, 320.28 KB)	Apply
13/152 Surgical interventions for renal stones	8 May 2014, by 1pm	Access commissioning brief (pdf, 123.64 KB)	Access guidance notes (pdf, 320.28 KB)	Apply
13/153 Ablative techniques for liver metastases	8 May 2014, by 1pm	Access commissioning brief (pdf, 121.76 KB)	Access guidance notes (pdf, 320.28 KB)	Apply

NIHR funding schemes

Health Technology Assessment

- The original NIHR programme
- Mainly funds trials evaluating 'technology'
- 'technology' = drugs, kit, psychological interventions, etc
- Expect a major trial to cost £1m+

NIHR funding schemes

Public Health Research

- Mainly evaluations of non-NHS interventions
- (Programme Director is Catherine Law of ICH)

NIHR funding schemes

Health Services and Delivery Research

- Evaluations of NHS services

NIHR funding schemes

Efficacy and Mechanism Evaluation (EME)

- Mainly evaluations of interventions but will also fund understanding scientific mechanisms
- (compared with HTA which is more pragmatic)

NIHR funding schemes

Programme Grants for Applied Research

- Funds programmes of work – several related projects (some of which may be a bit more upstream)
- £1-3m (+)

NIHR funding schemes

Research for Patient Benefit

- The ‘small grants’ scheme of NIHR
- Up to £350k
- Almost anything that would go to other programmes but that costs less
- Funds feasibility studies towards trials

NIHR funding schemes

Invention for Innovation

- The ‘dragon’s den’ of NIHR
- Present your case for early funding of new kit

NIHR costs

Research costs
- Mainly can include FEC
- RfPB paid to NHS trust (usually university sub-contract)
- Applied Programmes – no overheads

Treatment costs
- Paid by local trust

Support costs
- Paid by networks

NIHR funding schemes

- Currently trying to weld separate programmes into more coherent 'one-stop-shop'
- A common application form
- Common themed calls (surgery, antibiotic resistance, long-term conditions in children and young people)

NIHR funding schemes

- You can be an applicant/grant holder
- You can be a panel/committee member

NIHR funding schemes

- Website for more information

http://www.nihr.ac.uk