20 September 2018

IPD-Work studies on job strain and effort reward-imbalance at work as risk factors for morbidity and mortality

Mika Kivimäki
University College London
University of Helsinki

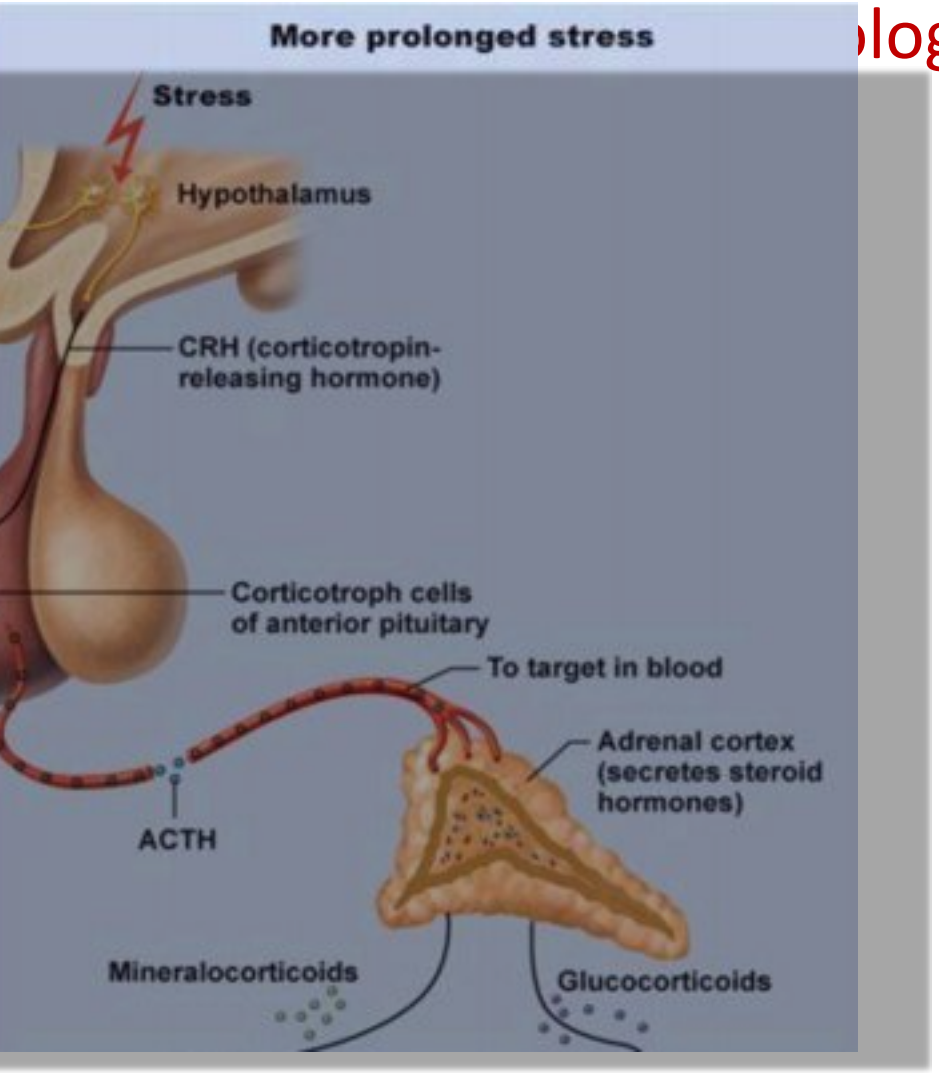
Outline

1. Why IPD-Work consortium was set up?

2. What have we found?

3. Reflections on critique by Mikkelson and Ingre

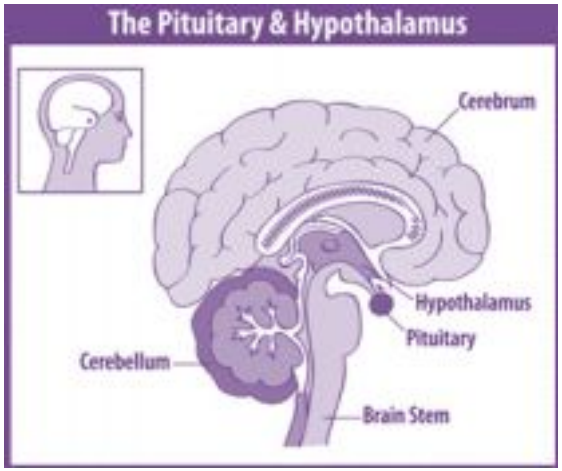
ological stress responses



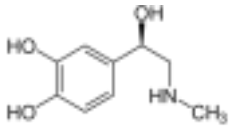
Stress perception

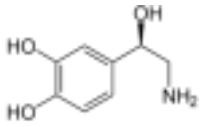
Changes in autonomic nervous system activate within seconds

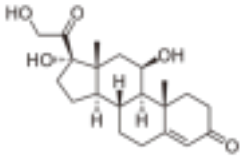
HPA-axis response activates within minutes



(adrenocorticotropic hormone)

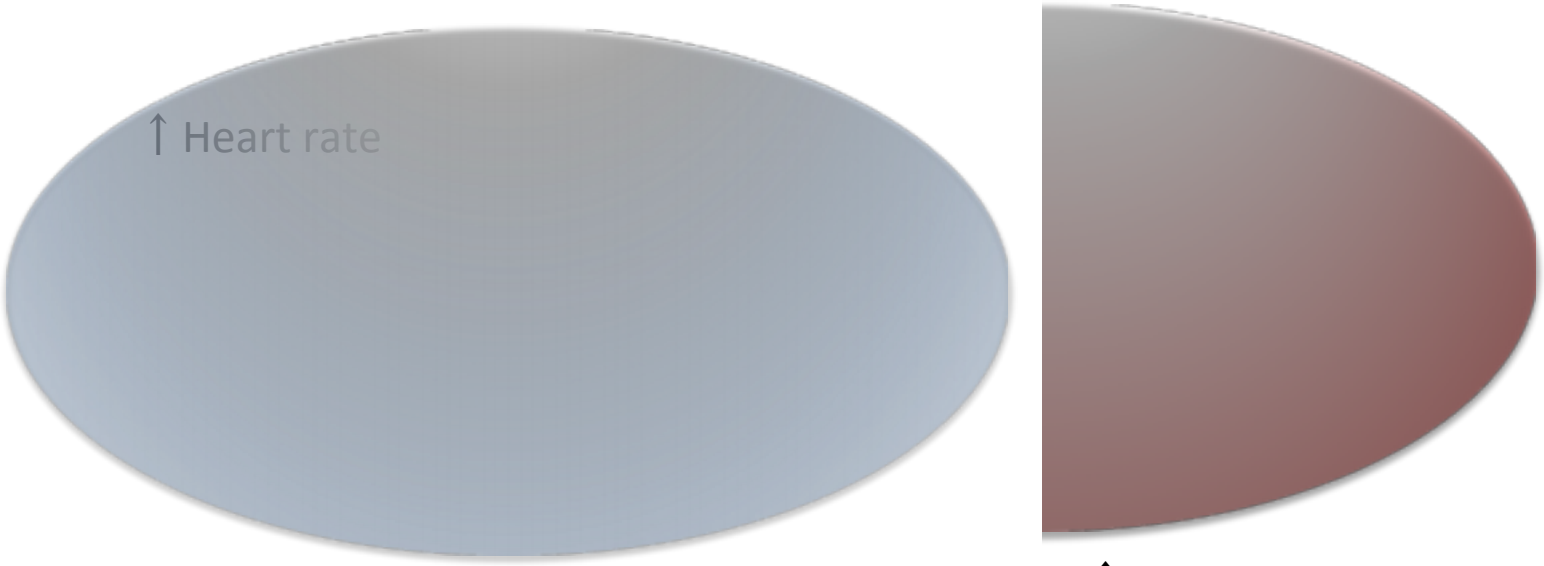
Epinephrine: 

Norepinephrine: 

Cortisol: 

Autonomic nervous system HPA-axis

'Rest-and-digest' → 'Fight-or-flight'



↑ Force of contraction
↑ Arrhythmias
↑ IL-6
↑ Bronchial passages

↓ Large intestine motility

↑ Blood pressure
↑ Coagulation
↑ Insulin resistance

↑ Glucose availability
↓ Immune response
↓ Protein synthesis

When stress response is harmful for health?

What organ systems are particularly vulnerable?

Cardiovascular system / Circulatory system

Digestive system / Excretory system
Endocrine system
Integumentary system/ Exocrine system
Lymphatic system / Immune system
Muscular system
Nervous system
Renal system / Urinary system
Reproductive system
Respiratory system
Skeletal system

2 principles in IPD-Work consortium

(1) Pooling individual-level data:

・Possible to detect small effects.
・With large datasets it is possible to show (and publish) absence of associations convincingly.
・Allows comparison of published and unpublished data.

NordForsk

NEW OSH ERA joint call for research proposals

on psychosocial risks at work

2010 – 2012 2015 – 2020

Kivimäki et al. *Int J Epidemiol* 2013

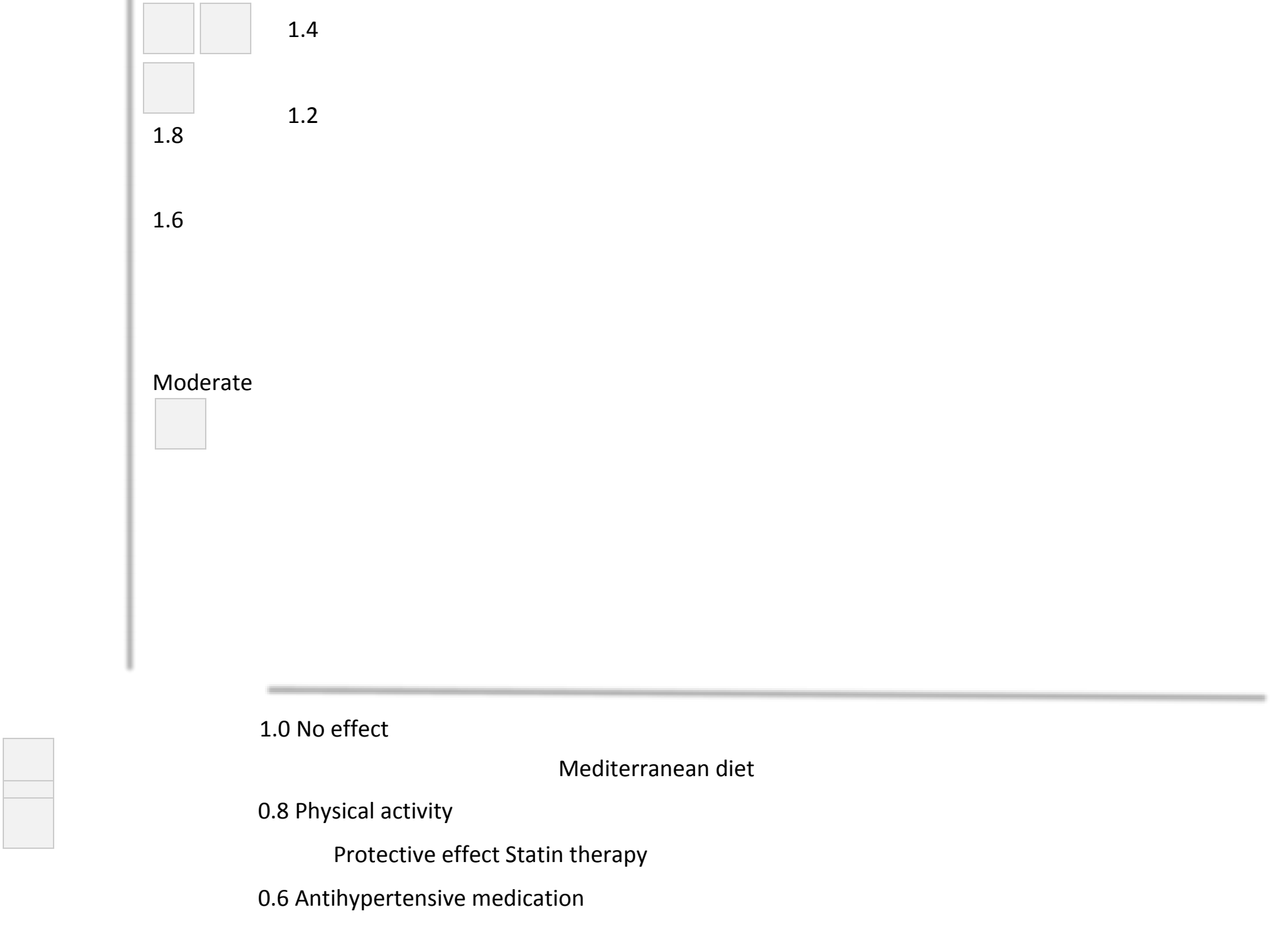
Reported stress effect cardiometabolic multimorbidity
Relative risk of CHD Comparison to other risk

factors 10 Extreme risk Morbid obesity for

2.4 Diabetes

Smoking, hypertension,

2.0 Major risk factor Obesity


1.4
1.2
1.8
1.6
Moderate
1.0 No effect
Mediterranean diet
0.8 Physical activity
Protective effect Statin therapy
0.6 Antihypertensive medication

Systolic blood pressure in relation to CVD mortality rates: the Prospective Studies Collaboration

Rory Collins

Systolic blood pressure in relation to CVD mortality rates: the Prospective Studies Collaboration

Rory Collins

Systolic blood pressure in relation to CVD mortality rates: the Prospective Studies Collaboration

Rory Collins

2 principles in IPD-Work consortium

(1) Pooling individual-level data:

- Possible to detect small effects.
- With large datasets it is possible to show (and publish) absence of associations convincingly.
- Allows comparison of published and unpublished data.

(2) Pre-defined protocols:

- A description of exposure definitions published before any linkage with outcome data.
- Associations with outcomes do not affect the way exposures are operationalised.

Kivimäki et al. *Int J Epidemiol* 2013

44 alternative measures of job strain

The availability of alternative ways of defining exposures can encourage multiple testing and further contribute to selective reporting and publication bias.

Fransson et al. 2012: 11 different sets of questions that had been utilised to measures high demands and low job control

Landsbergis et al 1994: multiple alternative ways of defining job strain when using identical item content: (1) the quotient, (2) the quadrant term, (3) the quadrant term using national means, and (4) linear term formulations.

Kivimäki et al. *Int J Epidemiol* 2013

1. Develop a "diagnostic procedure" for job

strain: Examination of 2 “symptoms” (high demand, low control)

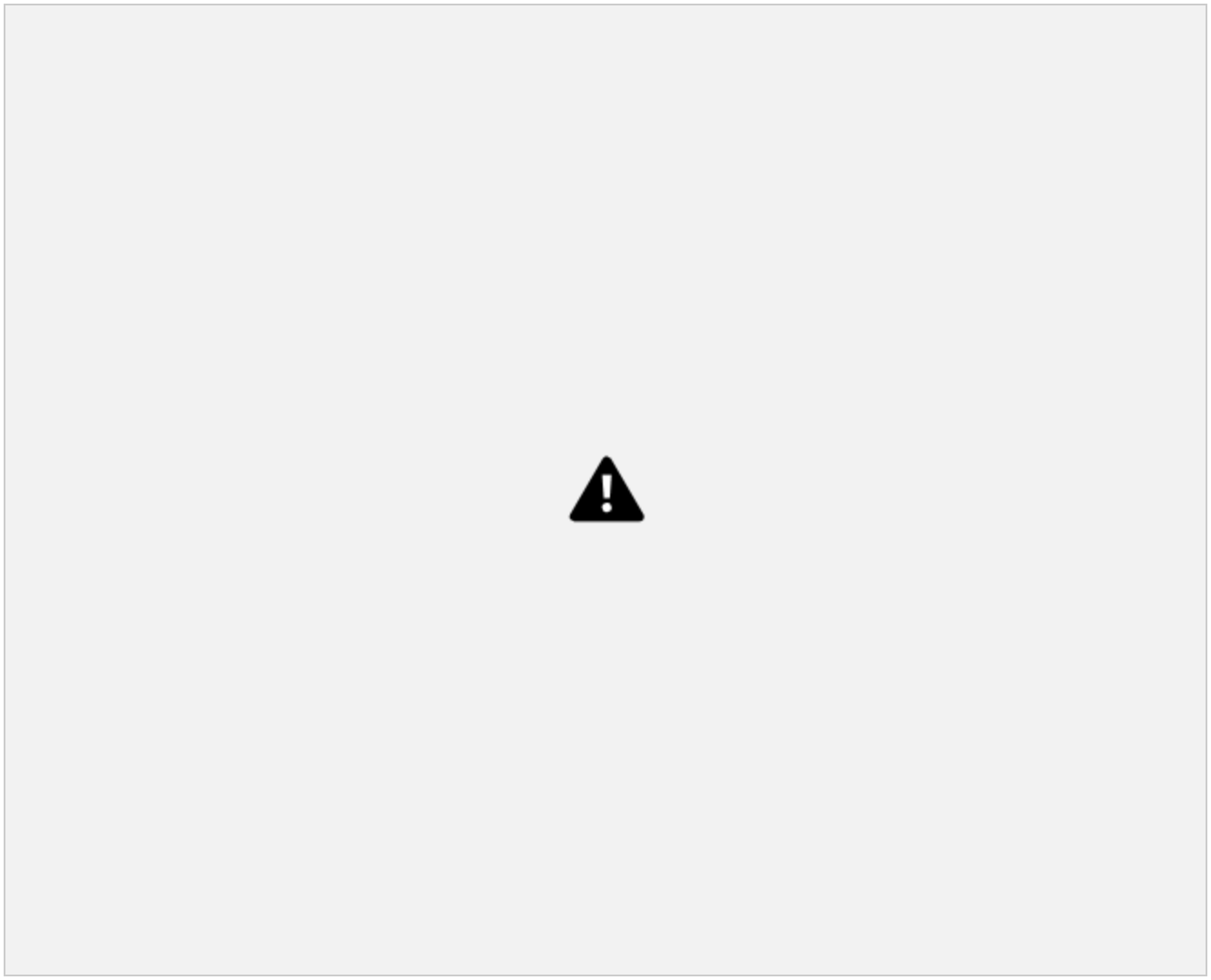
Job strain diagnosed if both symptoms are present

2. Conduct research on the outcomes of job

strain: Follow-up of people with and without “diagnosed” job

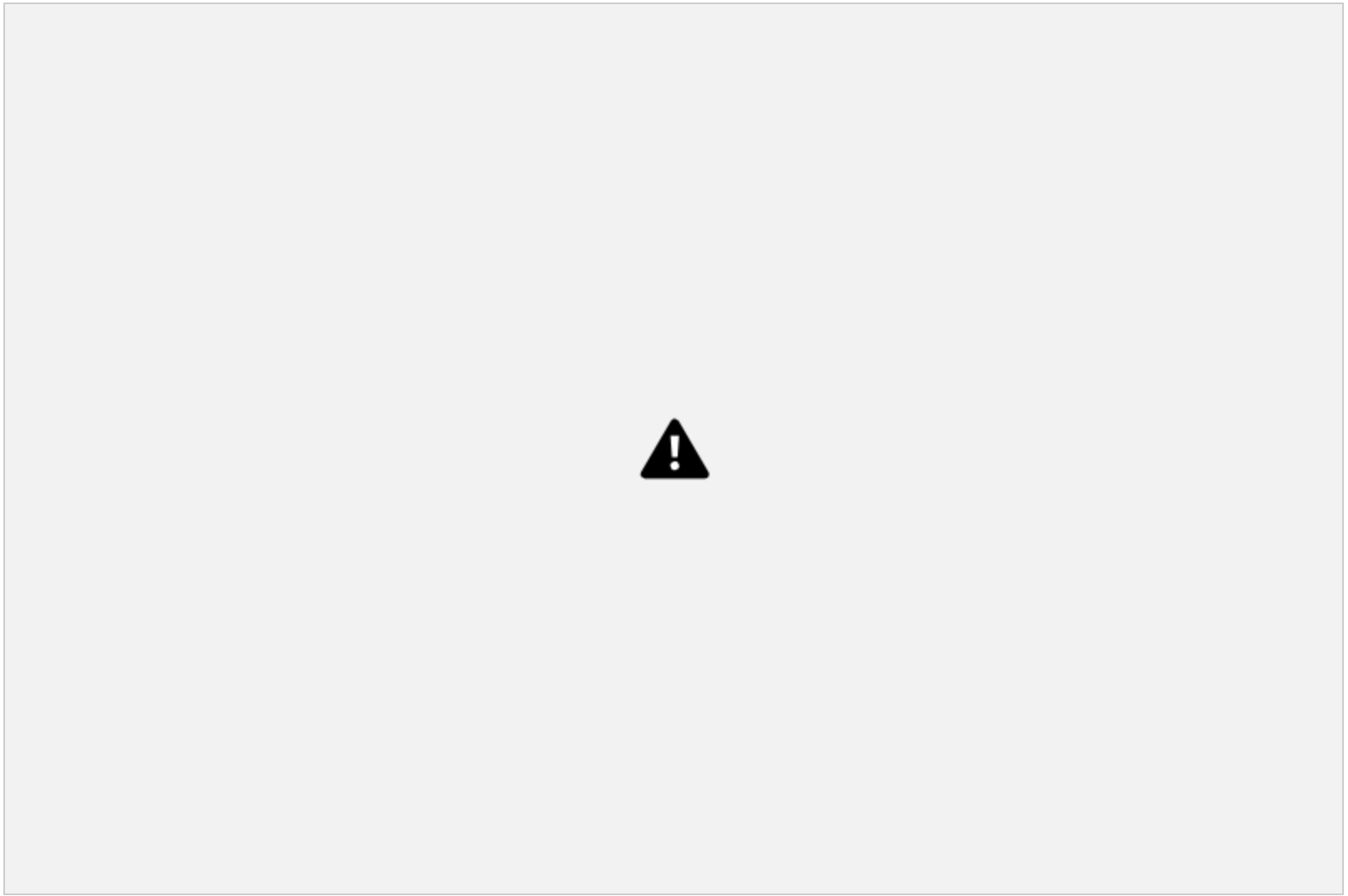
strain

Job strain defined as above median job demands combined with below median job control. No job strain refers to all other combinations



What have we found?

et al.



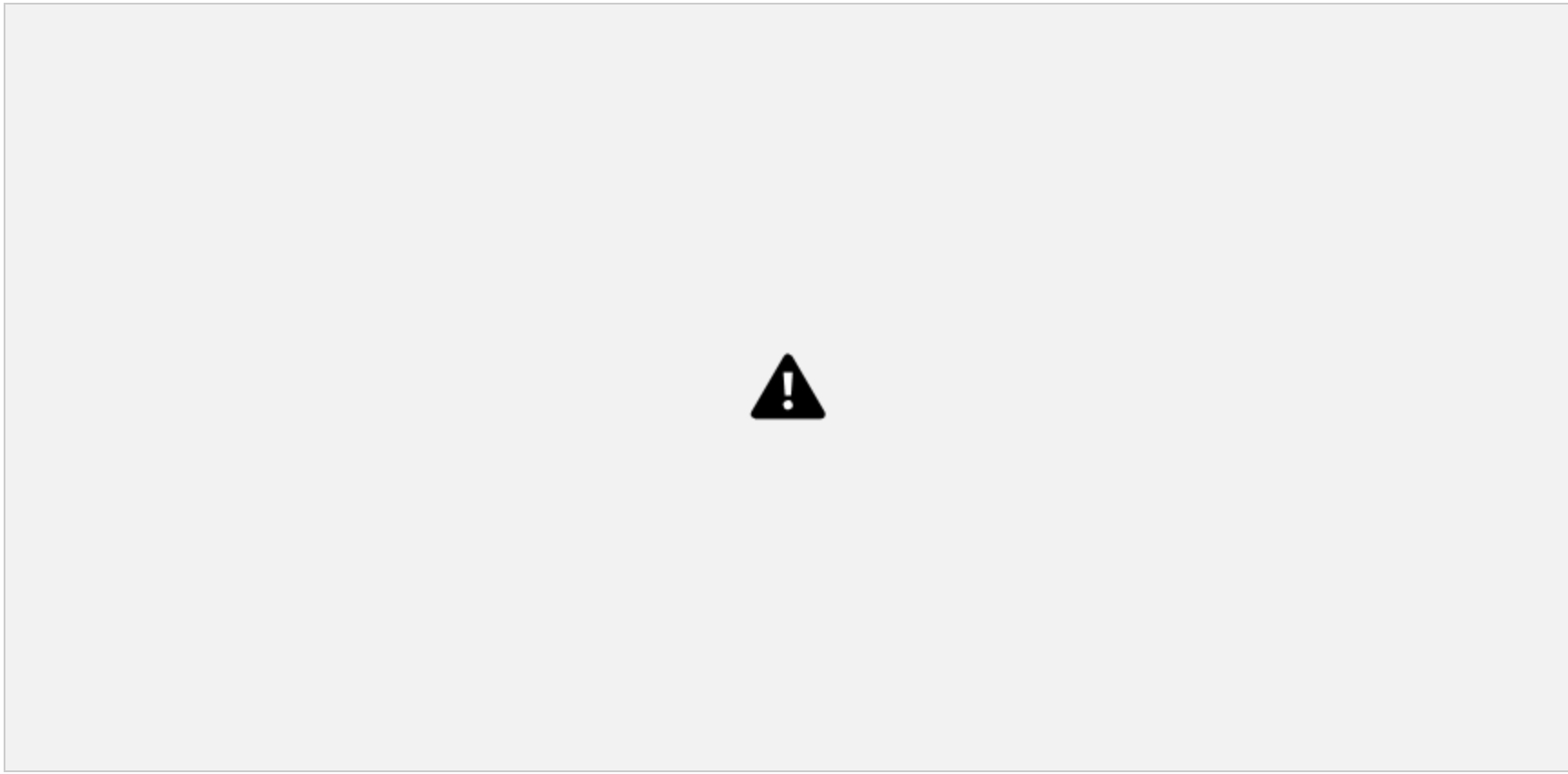
Kivimäki et al. *Lancet* 2012

Findings were robust to multivariable adjustments, exclusion of the

first years of follow-up and stratification by publication status and region

Kivimaki et al. *IPD-Work. Lancet 2012*

Findings replicated in subgroups



Kivimaki et al. *IPD-Work. Lancet 2012*

Stress and chronic disease in the general population

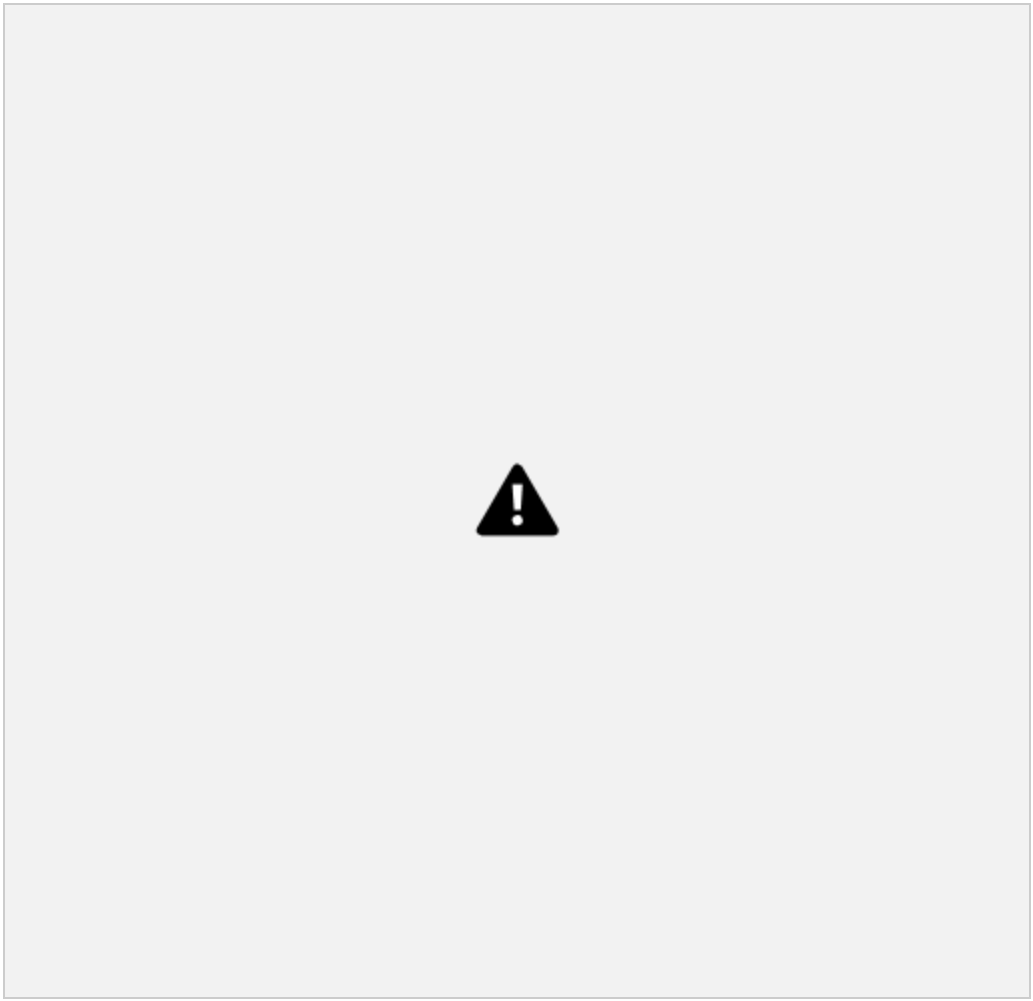
No association

Weak or moderate

Strong (RR > 2)

Very strong (RR > 5)

Kivimaki et al. *Nat Rev Cardiol* (2018)



What makes stress harmful for cardiometabolic

health? Normal Chronicity (‘allostatic load’)

McEwen *N Engl J Med* 1998

Stress

Indirect effect

Direct effect

prognosis

Triggering Effect on

pathology

Cardiac/cerebro vascular event

Recurrent event/ death

Risk factors

Vascular

Plaques

• Hypertension •

• Aortic stiffness •

Cardiac remodeling (LVH)

• Atherosclerosis •

Chronicity (‘allostatic load’) hypothesis

Kivimaki et al. *Nat Rev Cardiol* (2018)

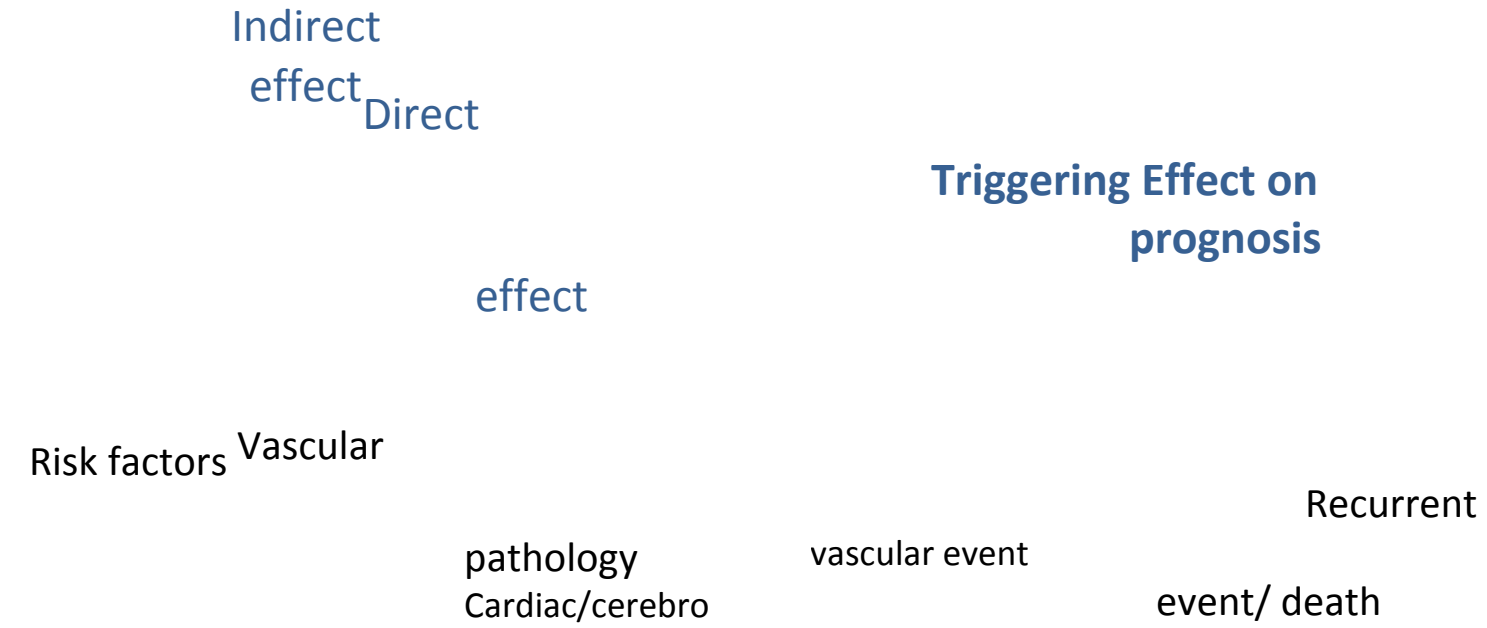
et al.

Independent associations of job strain and lifestyle factor with diabetes risk

What makes stress harmful for cardiometabolic health? Normal (A) Chronicity (‘allostatic load’)

e.g. those with cardiometabolic
)

Stress



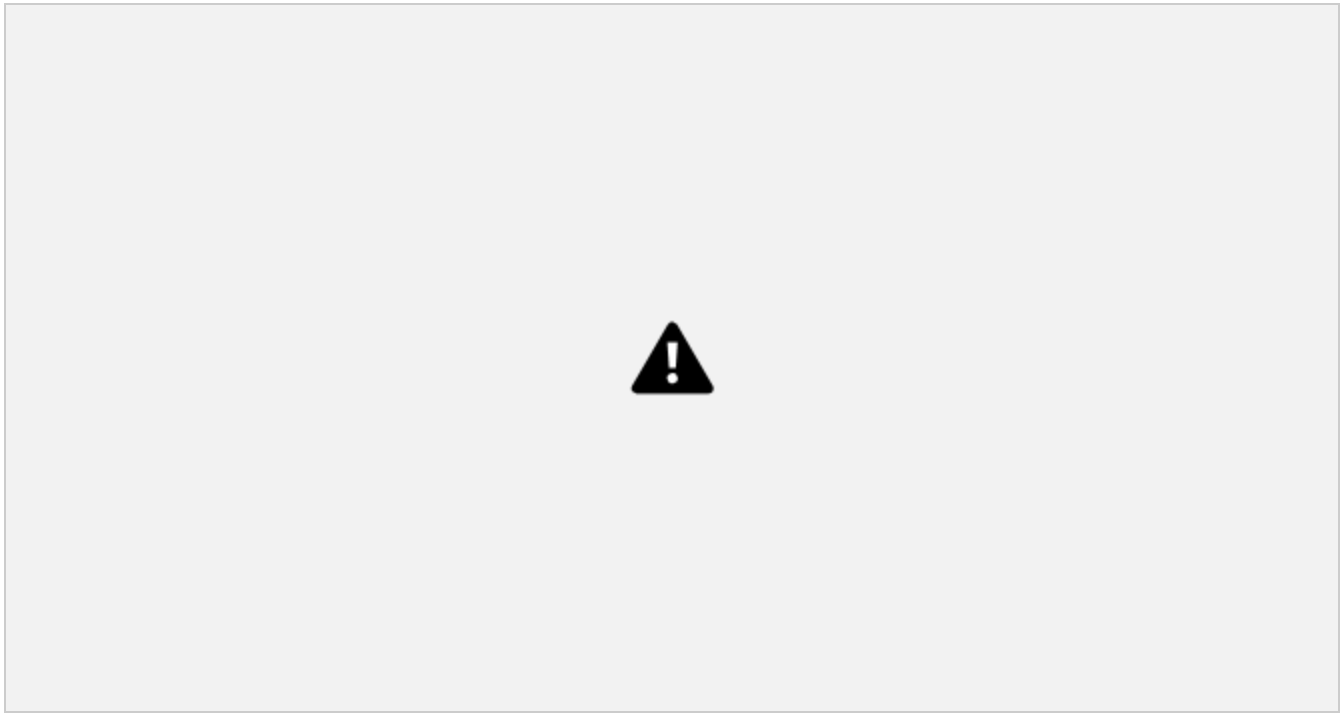
Kivimaki et al. *Nat Rev Cardiol* (2018)

Participants

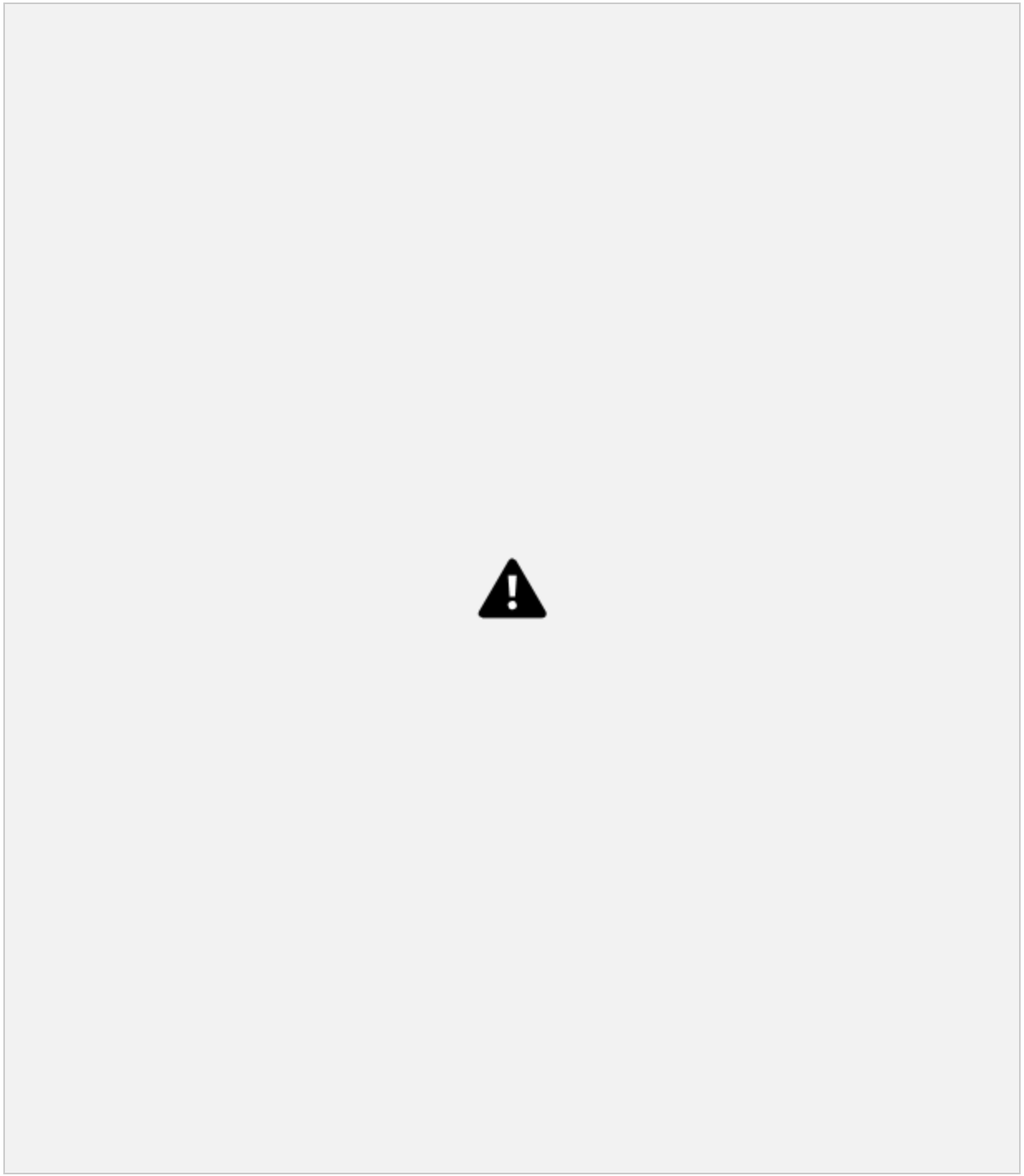
(*n*) Population Clinical outcome

Kivimaki et al. *Nat Rev Cardiol* (2018)

IPD-Work analysis of stress as a risk factor for death in vulnerable populations



Kivimaki et al *Lancet DE* 2018



Kivimaki et al *Lancet*

DE 2018

Stress

Indirect effect

Direct effect

prognosis

Triggering Effect on

pathology

Risk factors

Vascular

Cardiac/cerebrovascular event

Re

(1) High ambulatory blood pressure
(2) Thrombogenicity (blood clotting)
(3) Arrhythmia
(4) Inflammation

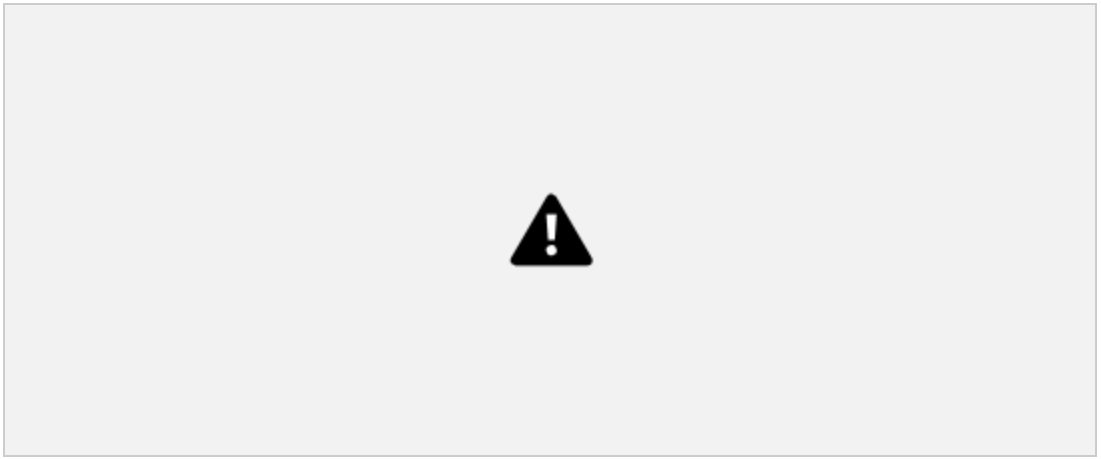
The general population **High-risk groups Patients with cardiovascular disease** Kivimaki et al.

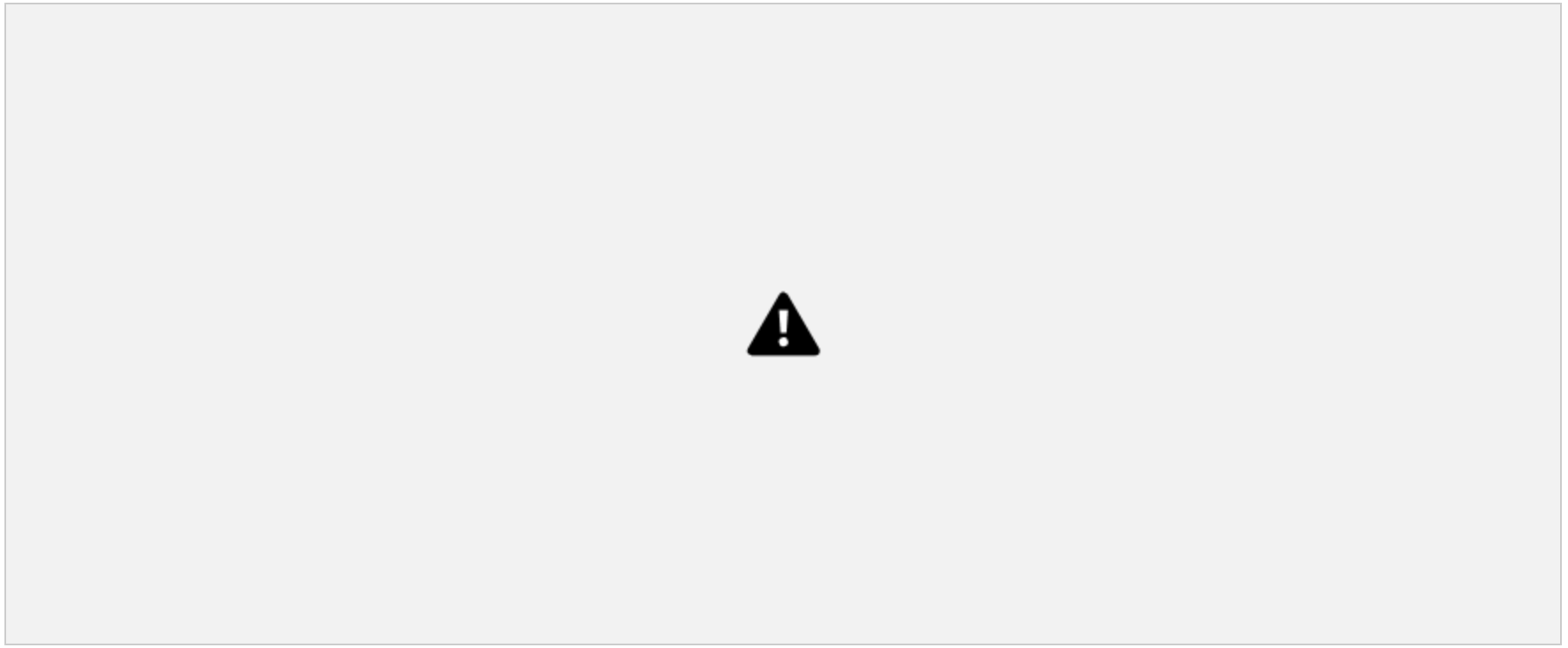
Nat Rev Cardiol (2018)

Stress and factors linked to disease triggering

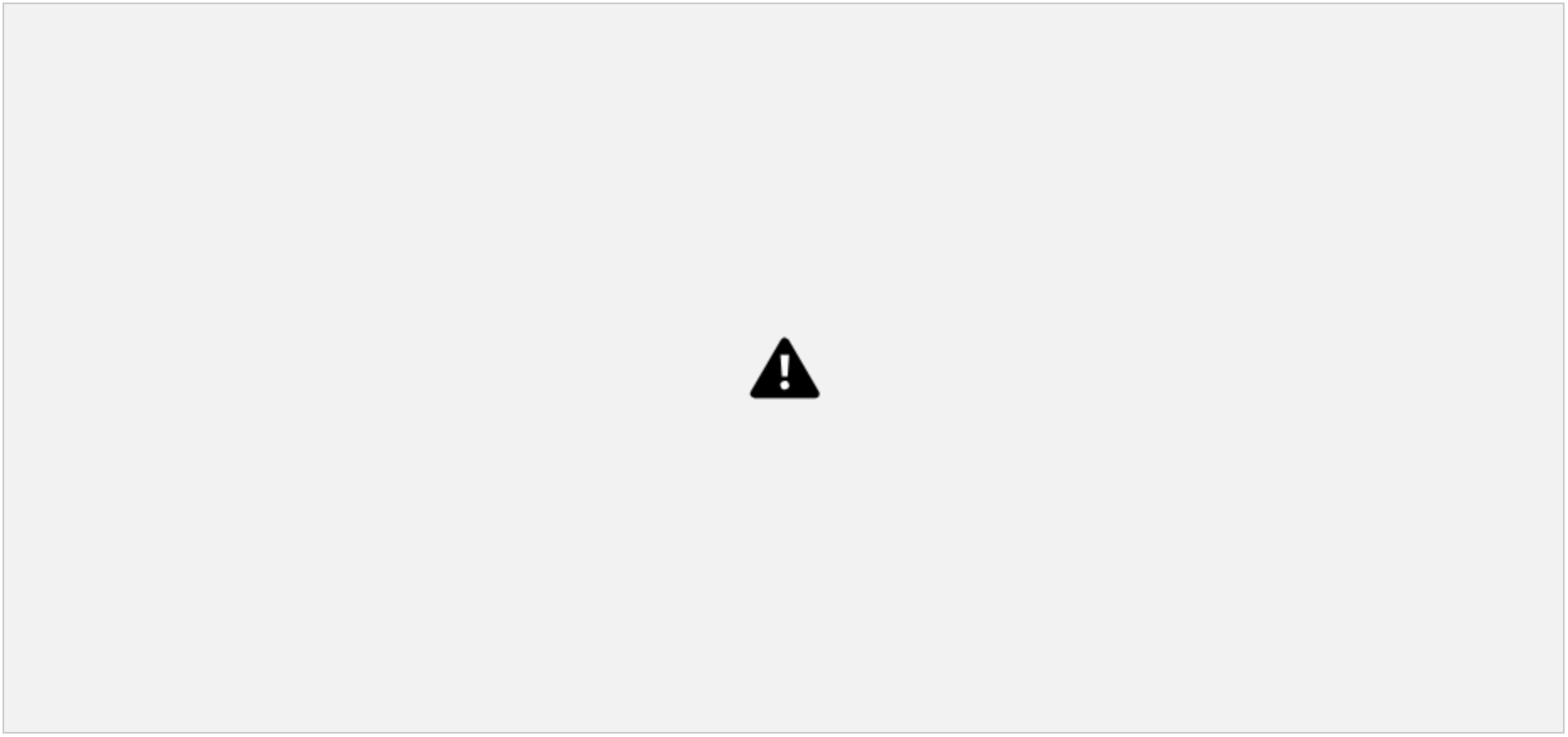
Kivimaki et al. *Nat Rev Cardiol* (2018)

Modifiability?





Richards et al. *Eur J Prev Cardiol* 2018

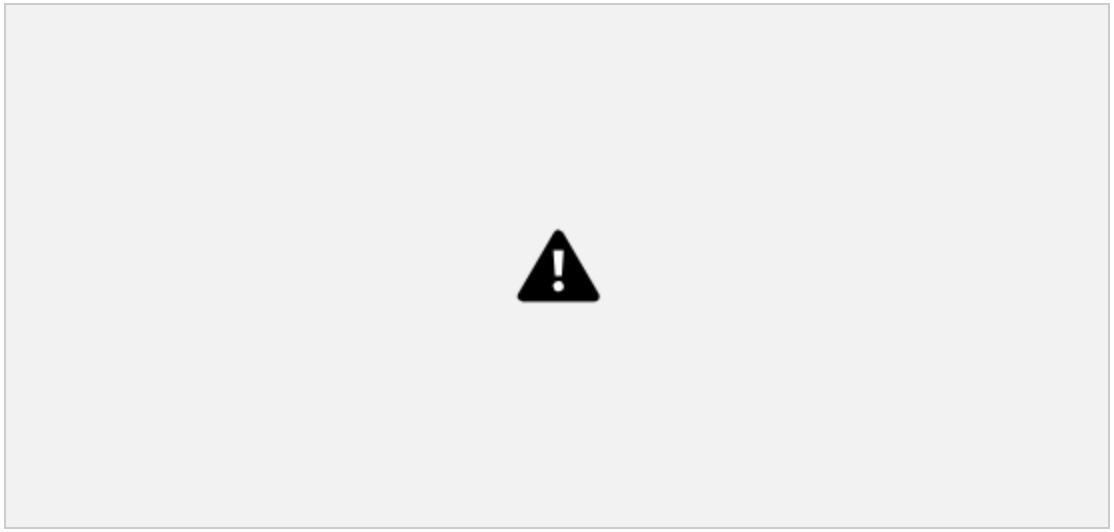


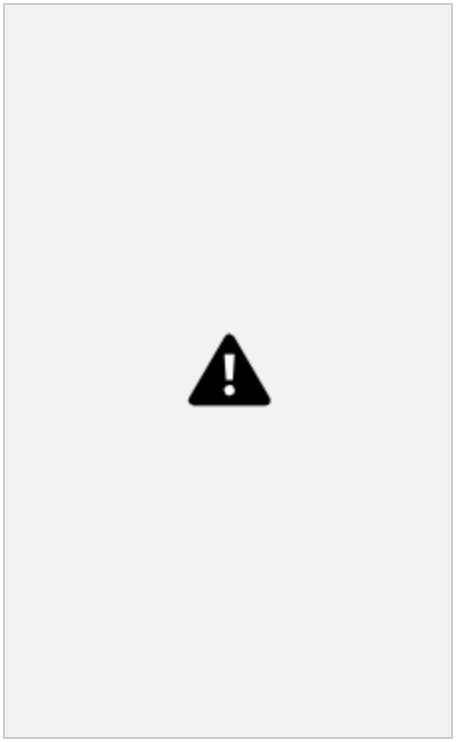
Richards et al. *Eur J Prev Cardiol* 2018

Critique

Balanced critiques:

“IPD-Work results are underestimates...





...or are overestimates."

A high-quality academic discussion?

1. Garcia et al.
   Epidemiol
   29(2);2018: Letter on the paper by Dragano et al. 2017

2. Siegrist et al. *Epidemiol* 29(2);2018: Author reply to Garcia et al.

2018.

3. Mikkelsen et al. *Epidemiol* 29(4);2018: Letter on the paper by Dragano et al. 2017

4. Dragano et al. *Epidemiol* 29(4);2018 Author reply to Mikkelsen et al. 2018

5. Ingre et al. *Epidemiol* Online First: (25 July 2018) Letter on the letter by Garcia et al. 2018 on the paper by Dragano et al. 2017 6. Choi et al.

Epidemiol Online First (26 July 2018): Letter on the letter by Ingre et al. 2018 on the letter by Garcia et al. 2018 on the paper by Dragano et al. 2017

CRITICAL THINKING:

- **Try to show that you are right.**

- **Try to show that your <u>opponent is wrong</u>.**

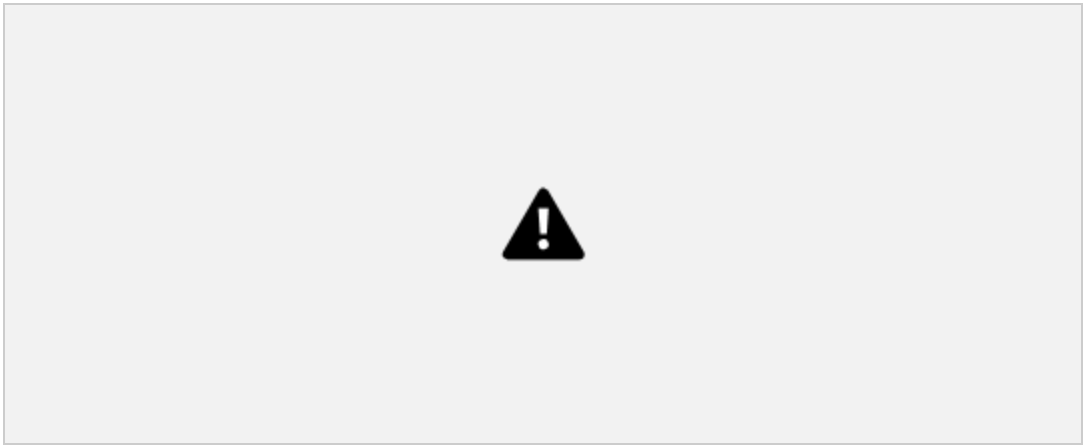
Reset and <u>look for the truth</u>.

- **Try to <u>prove yourself wrong</u> and accept your original standpoint only after having <u>failed</u> to do so.**

(Jarrick, 2017)

Do other scientists think that IPD-Work approach is flawed and that multiplicative interaction is the only correct approach?

No: The 50 authors of job strain papers do not think so.



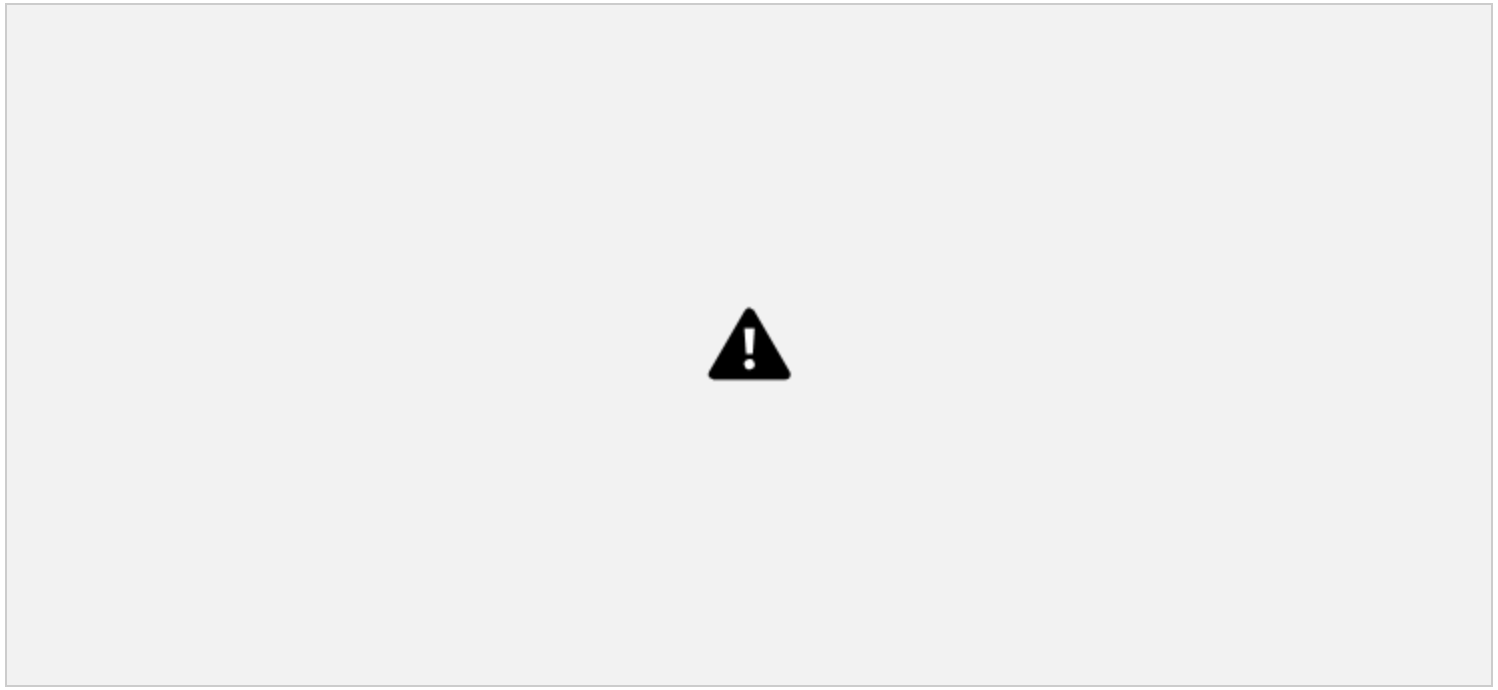
*"Seventy meta-analytic reviews met the eligibility criteria and provided **134** meta*

*analyses for associations from **1283** primary studies. While **109** associations were nominally significant (P < 0.05), only 8 met the criteria for **convincing evidence** and, when limited to prospective studies, convincing evidence was found in 6 (widowhood, physical abuse during childhood, obesity, having 4–5 metabolic risk factors, sexual dysfunction, **job strain**).”*

*I = convincing evidence

Do expert panels responsible for international clinical guidelines for cardiovascular disease prevention think that our approach is wrong and that multiplicative interaction is critical?

No:



Do those who developed the theoretical models agree with our operationalizations?

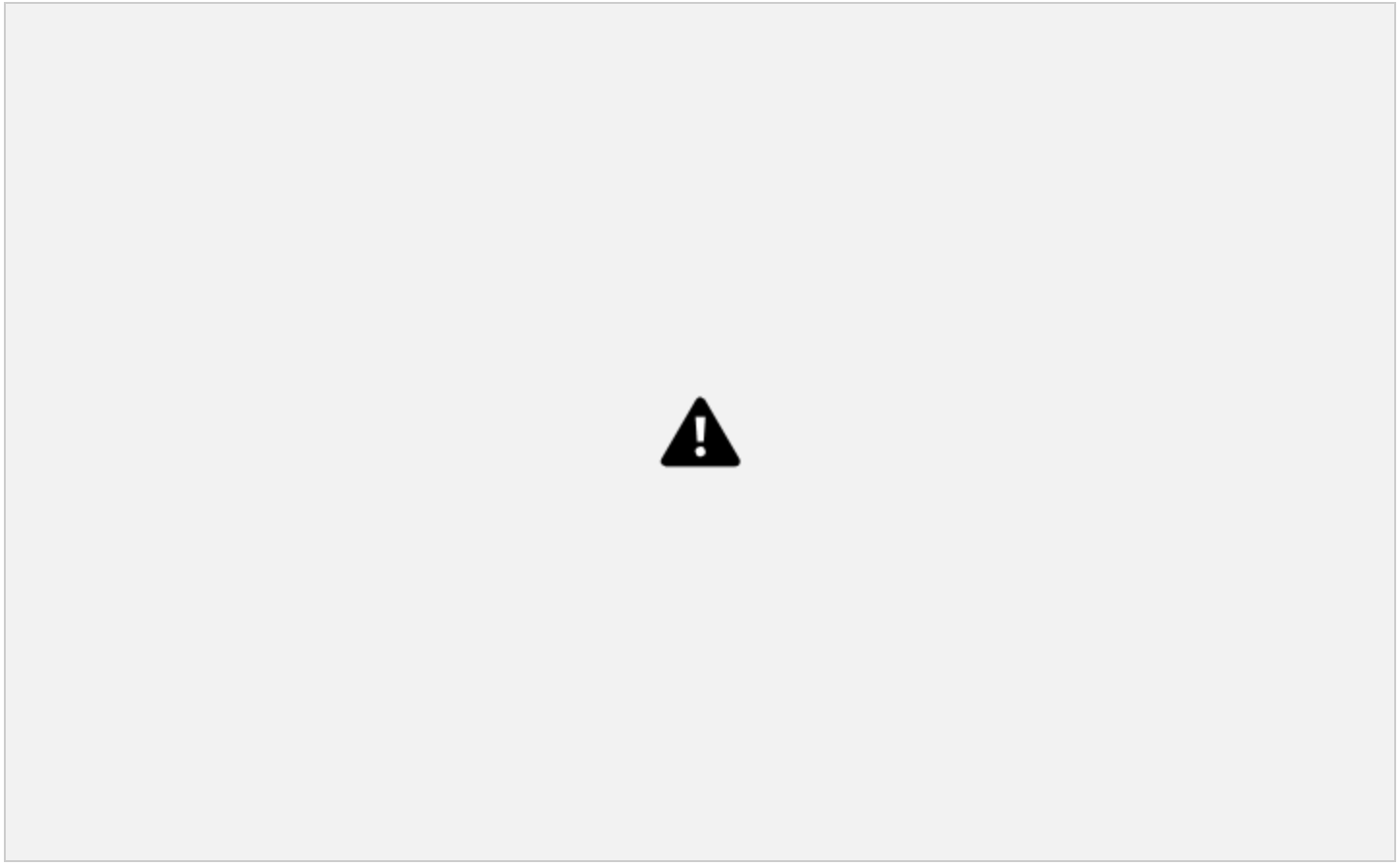
Yes: Siegrist, the person who generated the effort-reward imbalance model was the person who lead the development of the IPD-Work operationalization for effort-reward imbalance assessment.

Karasek, who developed the job strain model, has co-authored an IPD-Work paper on job strain and coronary artery disease, approving the way his concept was assessed.

Do those who have developed these theoretical models think testing multiplicative interaction is the only correct was to test their model?

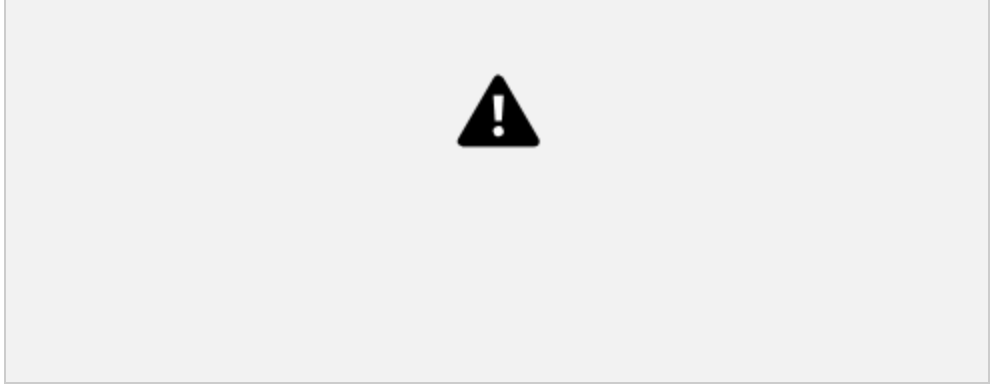
No: Siegrist writes to Mikkelsen that "*the effort–reward imbalance score is a simple ratio measure to identify persons whose efforts exceed their perceived rewards, irrespective of the strength of the deviation. In this scenario, multiplicative interaction tests are not needed*."

Karasek has been more vague, but his original evidence for the job strain model did not suggest a multiplicative interaction.



Karasek *Adm Sci Q* 1979

Odds ratio for job strain vs no job strain is 2.16 (95% CI 1.44-3.26)



Odds ratio for job strain vs no job strain is 2.61 (95% CI 1.77-3.85)

Karasek's original data from 1979 did not indicate multiplicative interaction

Low demands High demands High vs Low demands High strain vs other **Low control** 12.4 24.4 2.28 (1.38-3.76) 2.16 (1.44-3.26) **High control** 11.1 15.6 1.48 (0.86-2.54)

P(control*demand)=0.25

Modified data that would justify Mikkelsen and Ingre's job strain concept

Low demands High demands High vs Low demands High strain vs other **Low control** 12.4 30.8 3.14 (1.94-5.10) 2.98 (2.02-4.40) **High control** 11.1 15.6 1.48 (0.86-2.54)

p(interaction) = 0.25

30.0 20.0 10.0 0.0

Low control
High control
Low High
Job demands
High control Low control

Original data,

P(control*demand)=0.04

Low High
Job demands

High control Low control

Low control
High control

Summary

The ‘diagnostic procedure’ for job strain and effort-reward imbalance used in IPD-Work and numerous other studies is NOT seen as flawed by those who invented theoretical models.

Like job strain, diagnoses of many other conditions have a requirement of the presence of more than one symptom.

Establishing diagnosis before studying the outcomes of the diagnosed

condition is a standard procedure in medical science.

Changing the research question or diagnostic criteria after looking the outcomes is post-hoc science.