Can you really be fat and fit?
Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke

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HARVARD | **SCHOOL OF PUBLIC HEALTH**
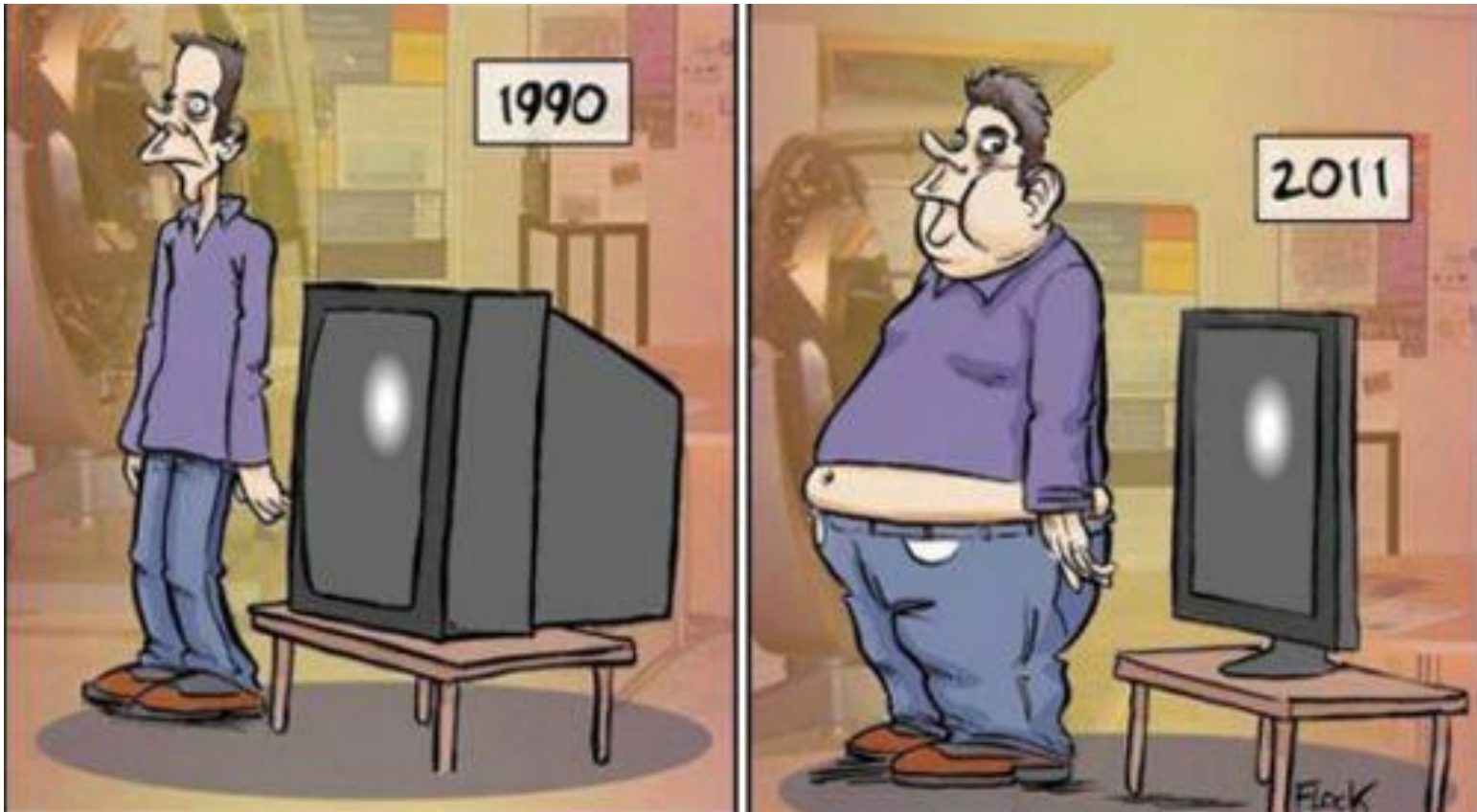
Department of Global Health and Population

Outline

- Background and motivation

- Methods

- Results

- Discussion

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- Background and motivation
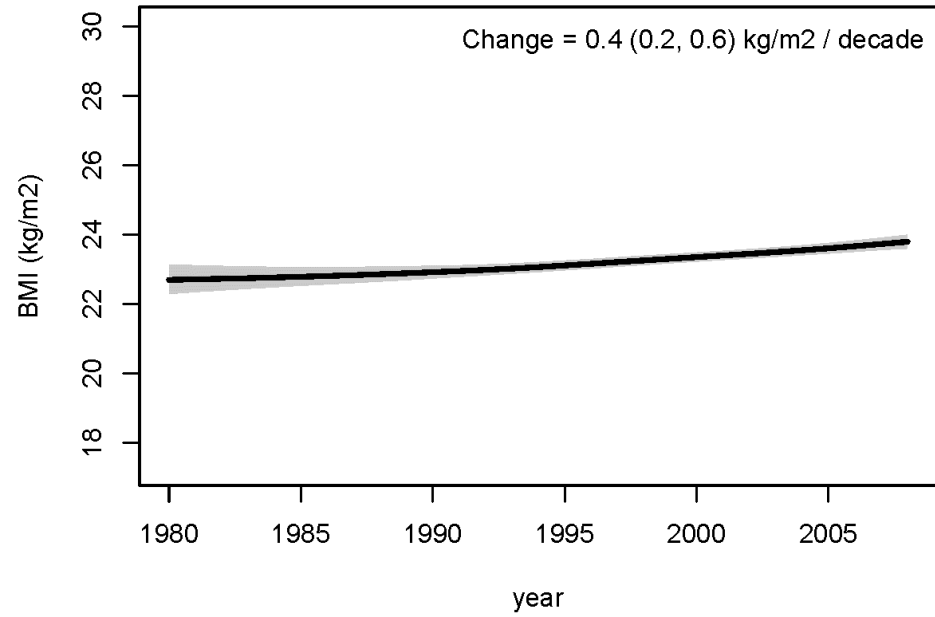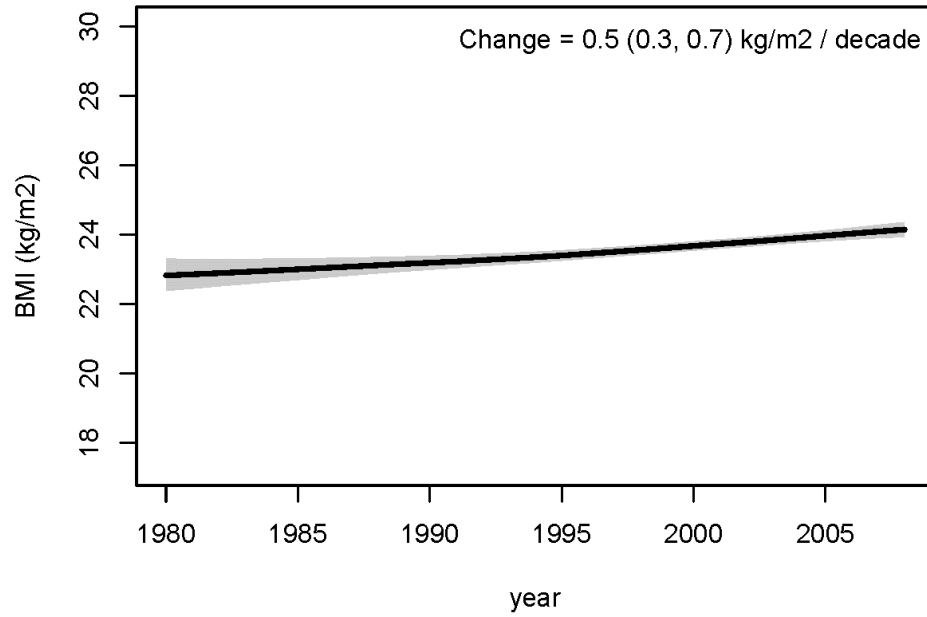- Methods
- Results
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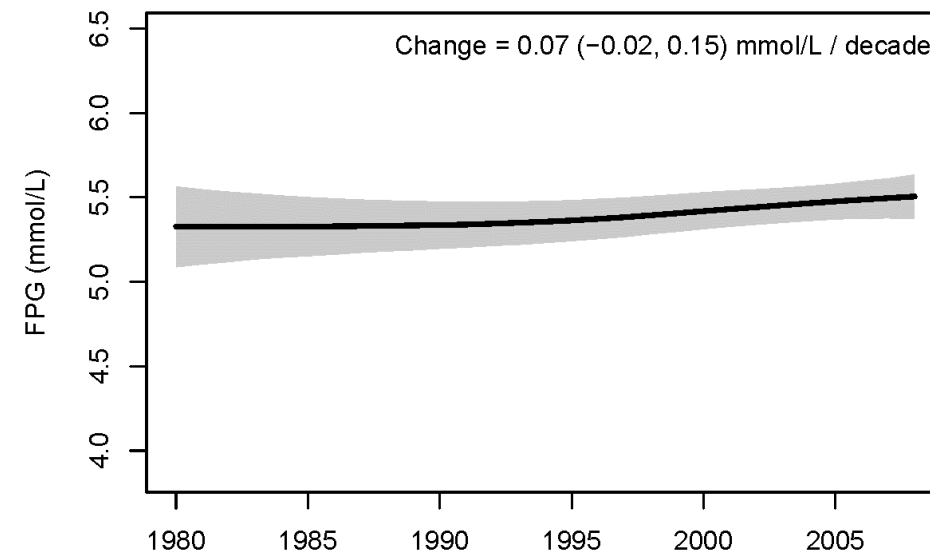# Global trends in obesity

Global trends in mean BMI

Women

Change = 0.5 (0.3, 0.7) kg/m2 / decade

BMI (kg/m2)

year

Men

Change = 0.4 (0.2, 0.6) kg/m2 / decade

BMI (kg/m2)

year

Finucane et al, Danaei et al. *Lancet* 2011

Global trends in mean BMI and FPG

Women

Men

Change = 0.5 (0.3, 0.7) kg/m2 / decade

Change = 0.4 (0.2, 0.6) kg/m2 / decade

Change = 0.09 (0.00, 0.17) mmol/L / decade

Change = 0.07 (−0.02, 0.15) mmol/L / decade

Finucane et al, Danaei et al. *Lancet* 2011

Global trends in mean SBP

Women

Change = −1.0 (−2.3, 0.3) mmHg/decade

Men

Change = −0.8 (−2.1, 0.4) mmHg/decade

Danaei et al. *Lancet* 2011
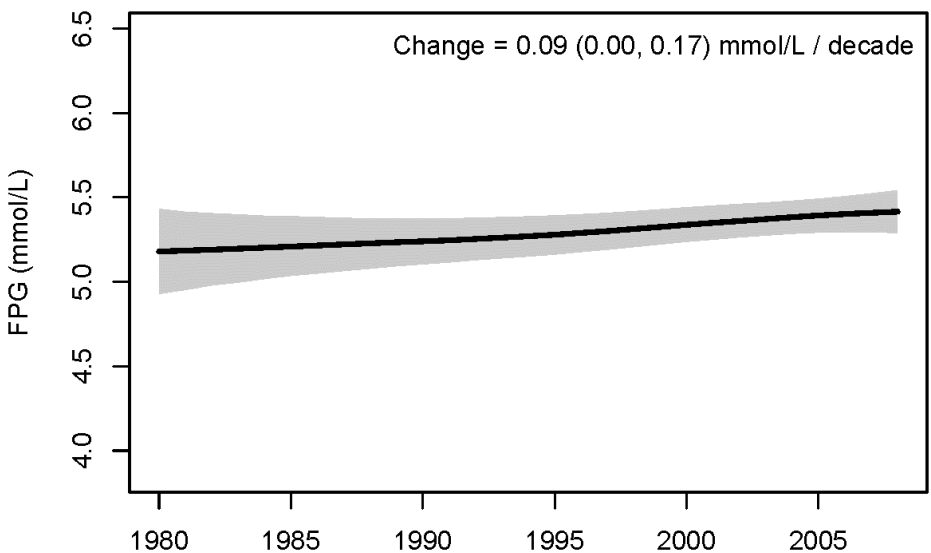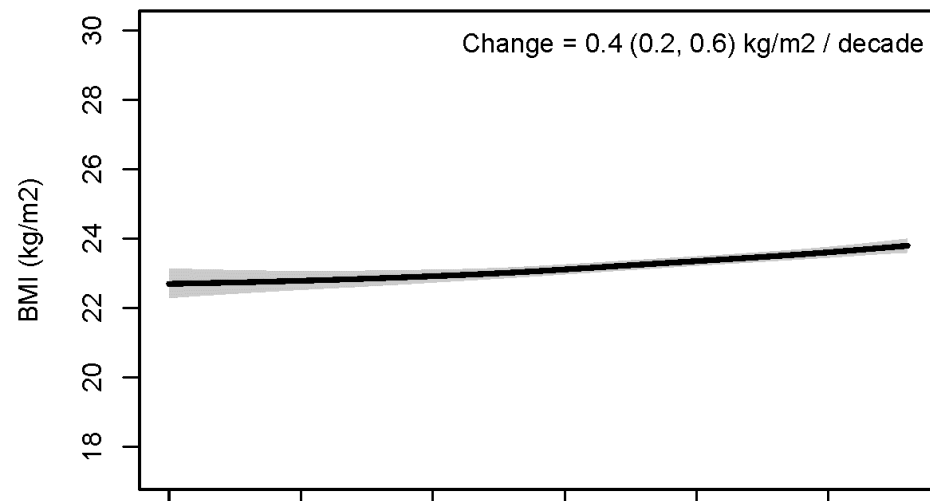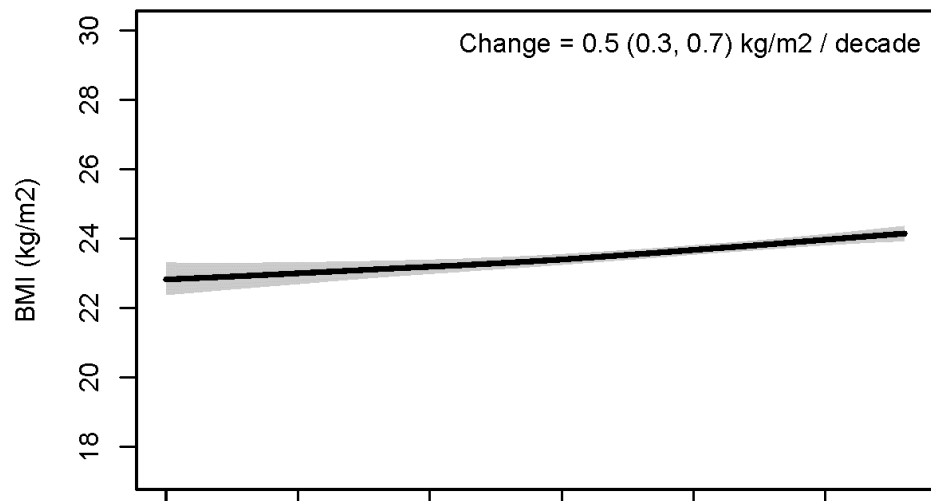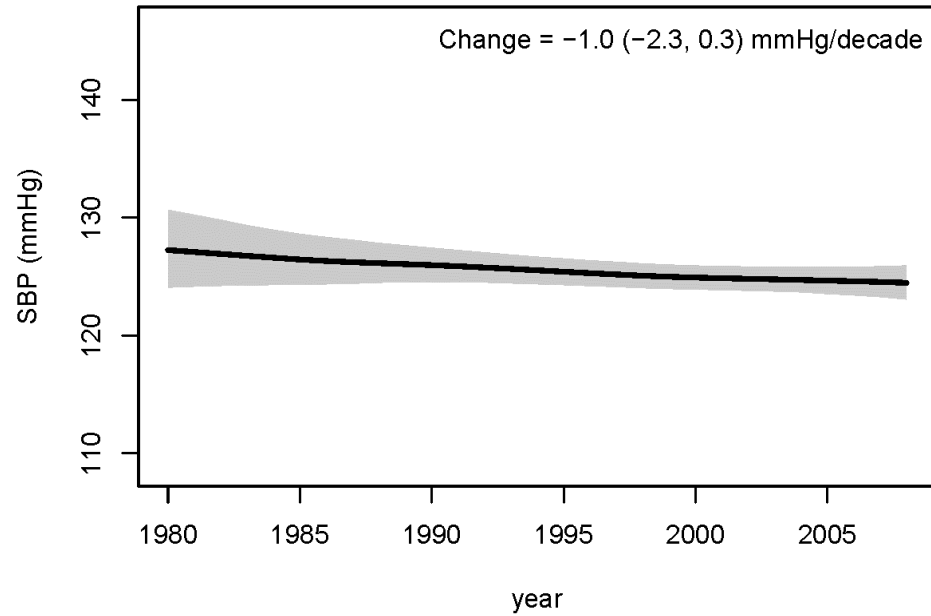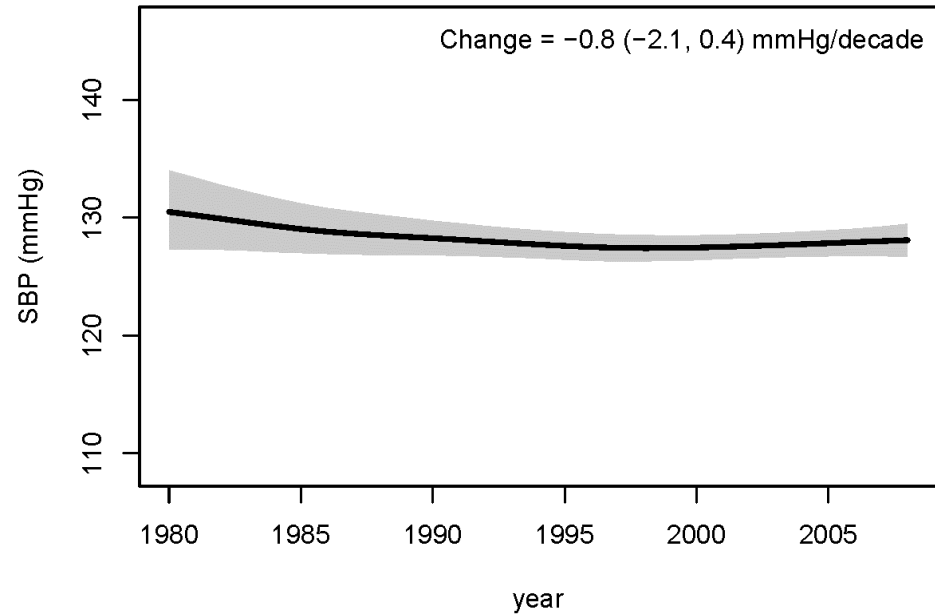
Global trends in mean SBP and TC

Women

Change = −1.0 (−2.3, 0.3) mmHg/decade

Change = −0.07 (−0.17, 0.03) mmol/L / decade

Men

Change = −0.8 (−2.1, 0.4) mmHg/decade

Change = −0.08 (−0.16, 0.00) mmol/L / decade

Danaei et al. Farzadfar et al *Lancet* 2011
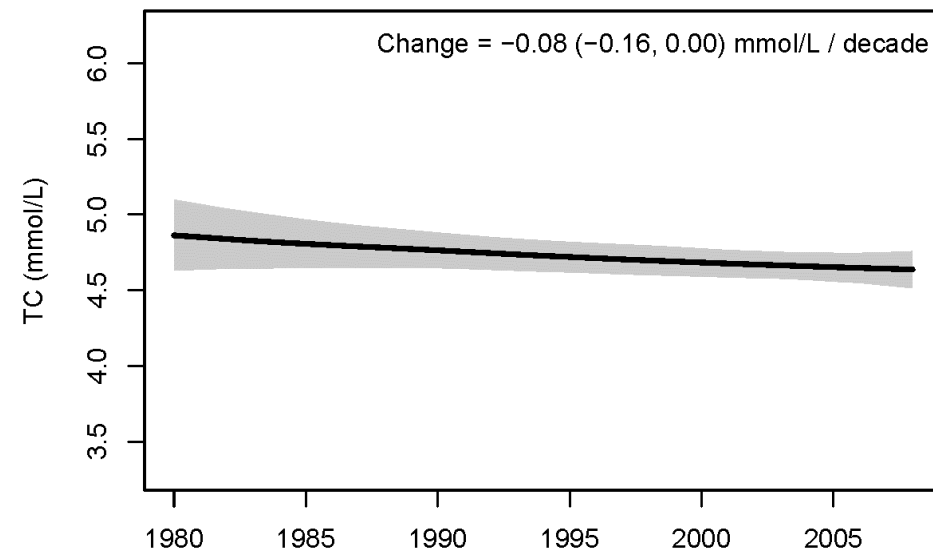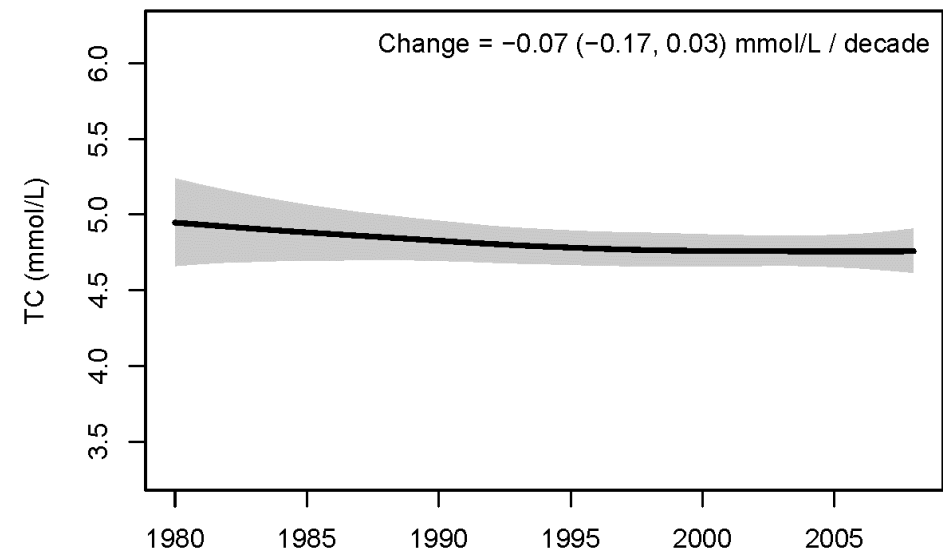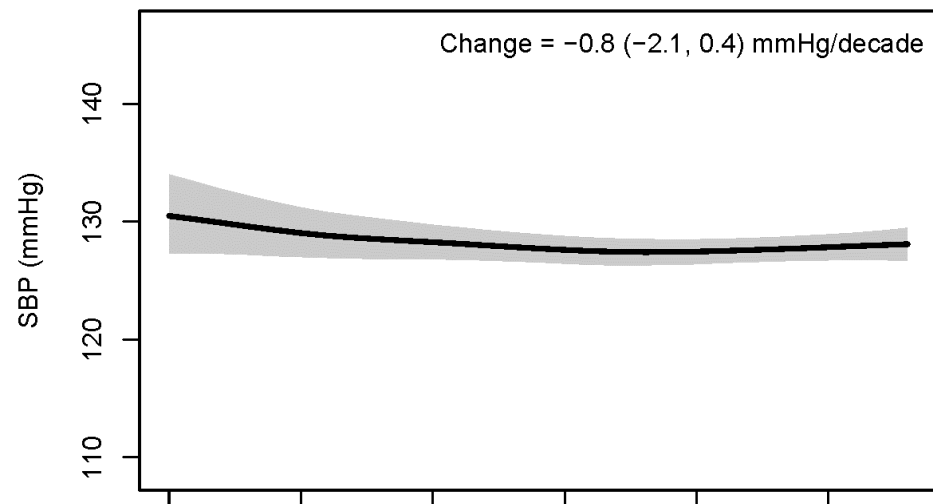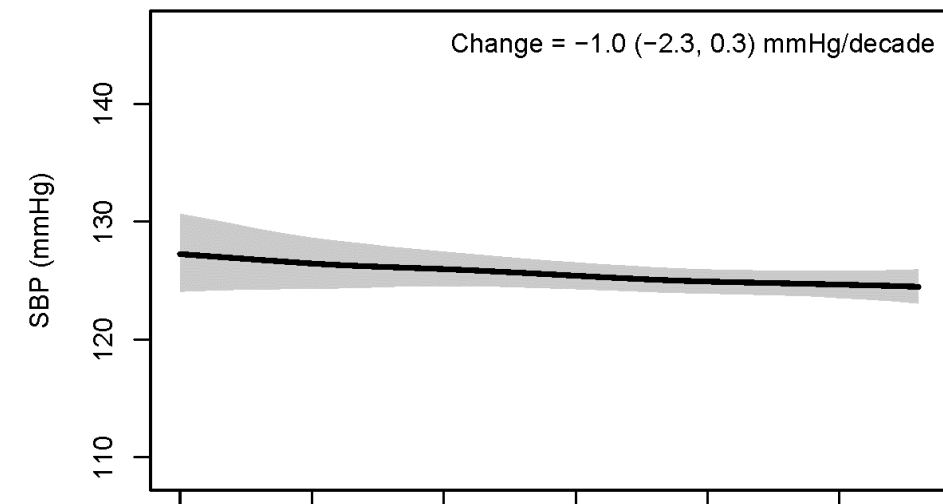
Associations of BMI with metabolic risks

The Prospective Studies Collaboration *Lancet* 2009
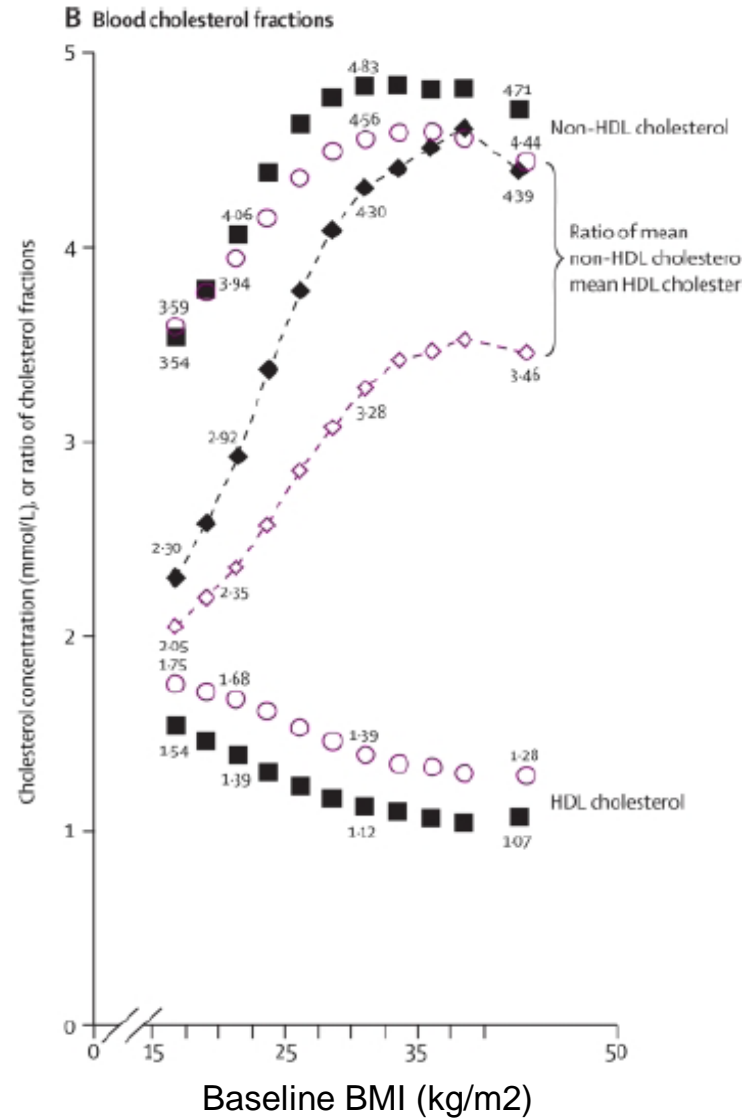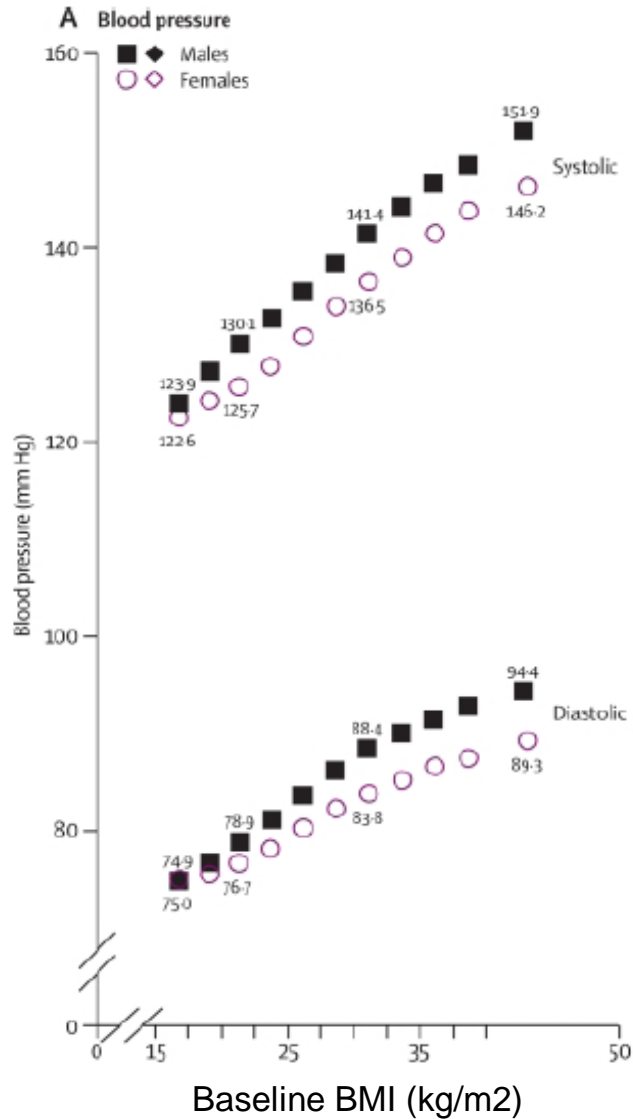
(Directed Acyclic) Causal Graph
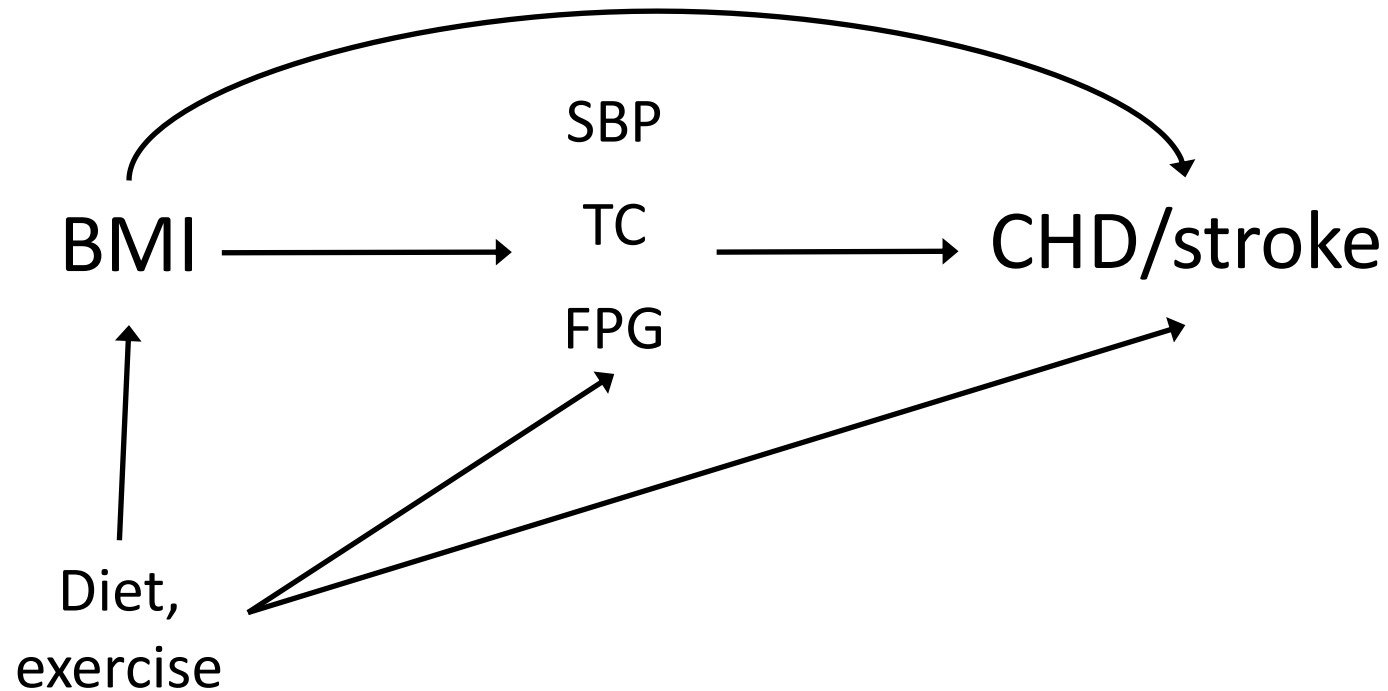
SBP: systolic blood pressure; TC: Total cholesterol; FPG: fasting plasma glucose

Associations of adiposity with CVD outcomes
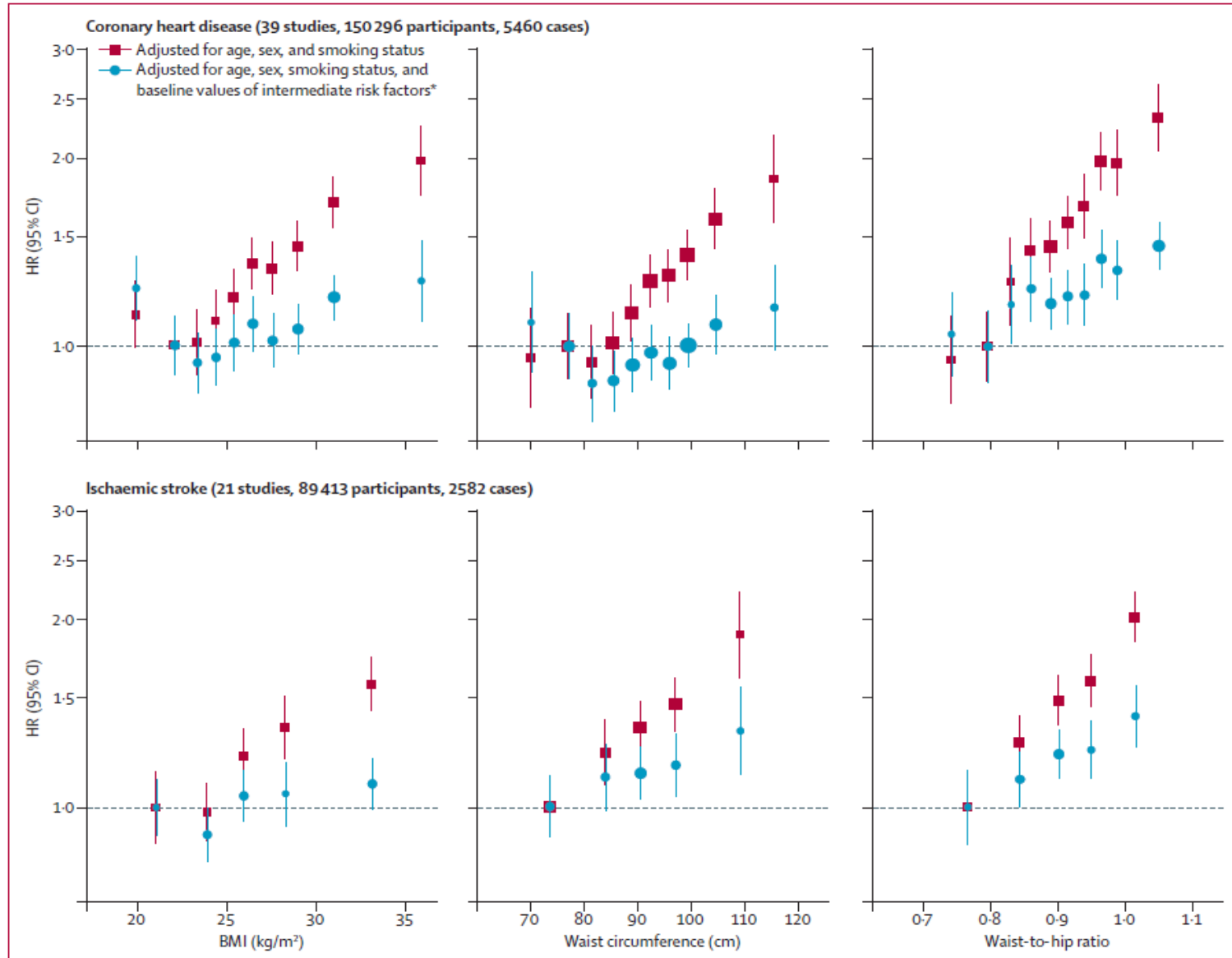
Previous analyses of mediated effect of adiposity

- A meta-analysis of 21 studies (Bogers et al, 2010)
  - Assess the effect of overweight on CHD mediated by blood pressure and cholesterol
- Few other prospective studies
  - Hedblad 2002, Jee 2006, Wilson 2008, The Emerging Risk Factors Collaboration, 2011
- Limitations:
  - Did not quantify the role of individual mediators or all possible combinations of two mediators
  - Did not assess whether characteristics of study populations influence the extent of mediation

Study objective

To quantify how much of the effects of excess body mass index (BMI) on coronary heart disease (CHD) and stroke are mediated through blood pressure, cholesterol, and glucose.

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Study selection

- A systematic search of prospective studies from MEDLINE and EMBASE (up to March 2010)

(1) prospective design with at least 1 year of follow-up

(2) participants were not selected based on prior history of CHD or stroke

(3) height and weight were measured (not self-reported) at baseline

(4) at least one of the mediators (blood pressure, serum cholesterol, and blood glucose or diabetes) was also measured at baseline

(5) fatal and/or non-fatal CHD or stroke were ascertained during follow-up

SAPHIR

12,857 Articles identified in search
5,710 From MEDLINE
7,147 From EMBASE

18 Articles from reference list

12,875 Articles identified

8,125 Articles excluded based on title and abstract review, 3656 articles excluded because of duplicates

1,094 Articles remaining after exclusion based on title and abstract review

414 Articles excluded based on full text review, and 148 articles excluded because we could not retrieve the full-text, and 18 because we could not translate the article

514 Articles remaining after exclusion based on full text review

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Data synthesis and study characteristics

- Requested re-analysis of data if an included article did not report the quantities of interest

- 61 prospective cohort studies re-analyzed by collaborators, 36 cohorts through request to the NHLBI or personal communication, with total of 1.8 million participants
  - Follow-up ranging from 2.7 to 43 years
  - A total of 57,161 CHD events and 31,093 stroke events
  - All 97 cohorts had measured BMI, 17 had waist circumference, or waist-hip-ratio;
  - 72 cohorts had all 3 mediators
  - 88 cohorts had CHD, 86 cohorts had stroke.

Number of cohorts by region

Region	Number of cohorts
East and Southeast Asia	33
Western Europe	32
North America	15
Australia or New Zealand	10
Latin America, Central/Eastern Europe and North Africa/Middle East	7
Total	97

Analytical approach

- Analyzed each cohort separately using Cox proportional hazards model.

- Fit 7 models for each outcome (CHD/stroke):
  - One with exposure and confounders (age, sex and smoking in all cohorts plus additional confounders such as diet, alcohol and exercise where available)
  - Six models with exposure, confounders and mediators (one at a time, 3 combinations of two mediators, all 3 mediators)

- Pooled the hazard ratios for total and direct effect using random effect models.

Metrics of mediation

- Percentage of Excess Risk Mediated (PERM)

Percentage of excess risk mediated (PERM)

$$= \frac{HR_{(confounder\ adjusted)} - HR_{(confounder\ and\ mediator\ adjusted)}}{HR_{(confounder\ adjusted)} - 1} * 100\%$$

- Analytical question: the study-specific uncertainty of these metrics

Uncertainty of metrics of mediation

- We randomly drew 5000 pairs of HR$_{\text{(confounder adjusted)}}$ and HR$_{\text{(confounder and mediator adjusted)}}$ from their corresponding uncertainty distributions while accounting for their correlations;

- We estimated PERM for each pair of HRs and quantified its variability across all 5000 estimates.

- We used the median of these 5000 estimates as the point estimate of PERM, and its 2.5[th] and 97.5[th] percentiles as the 95% confidence interval.
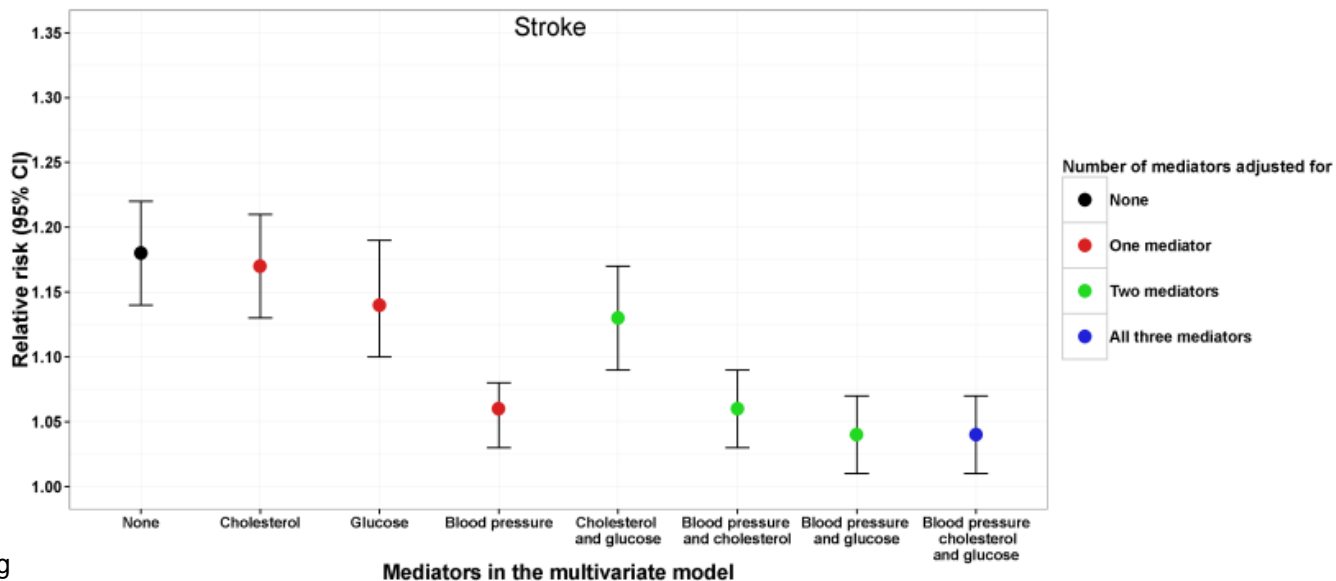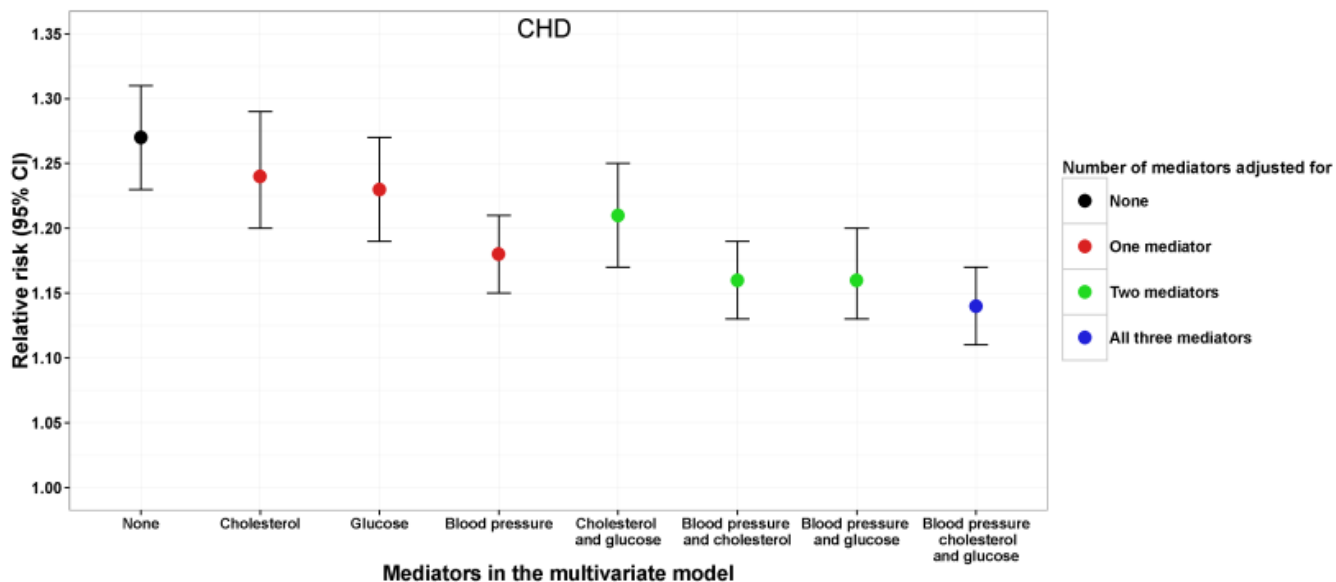
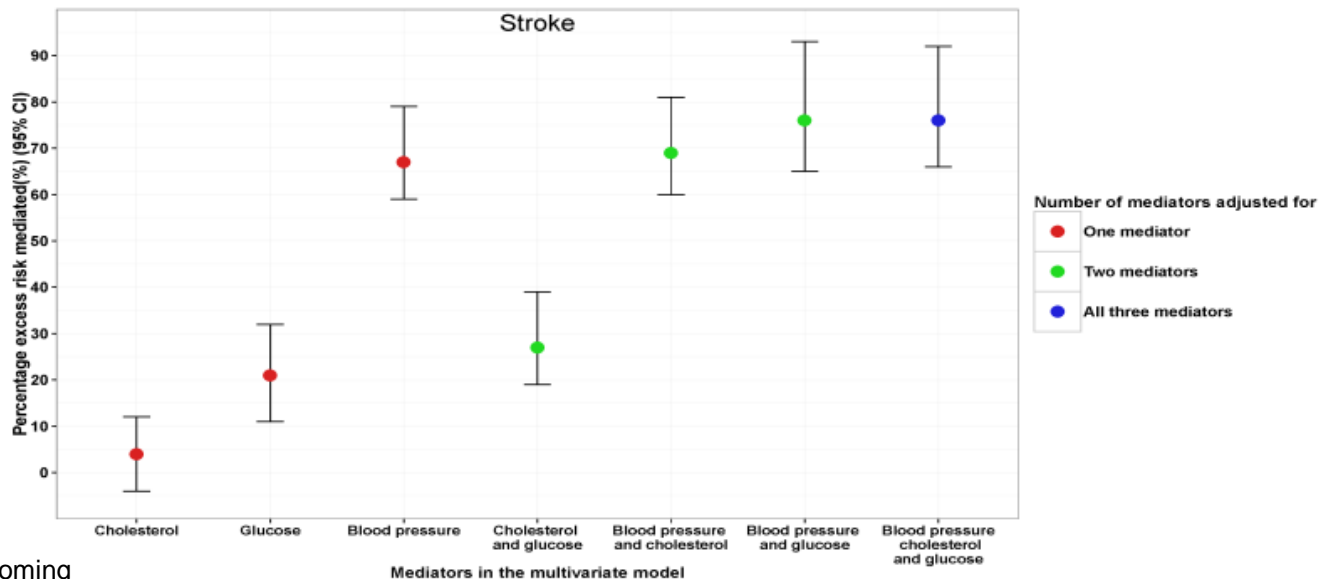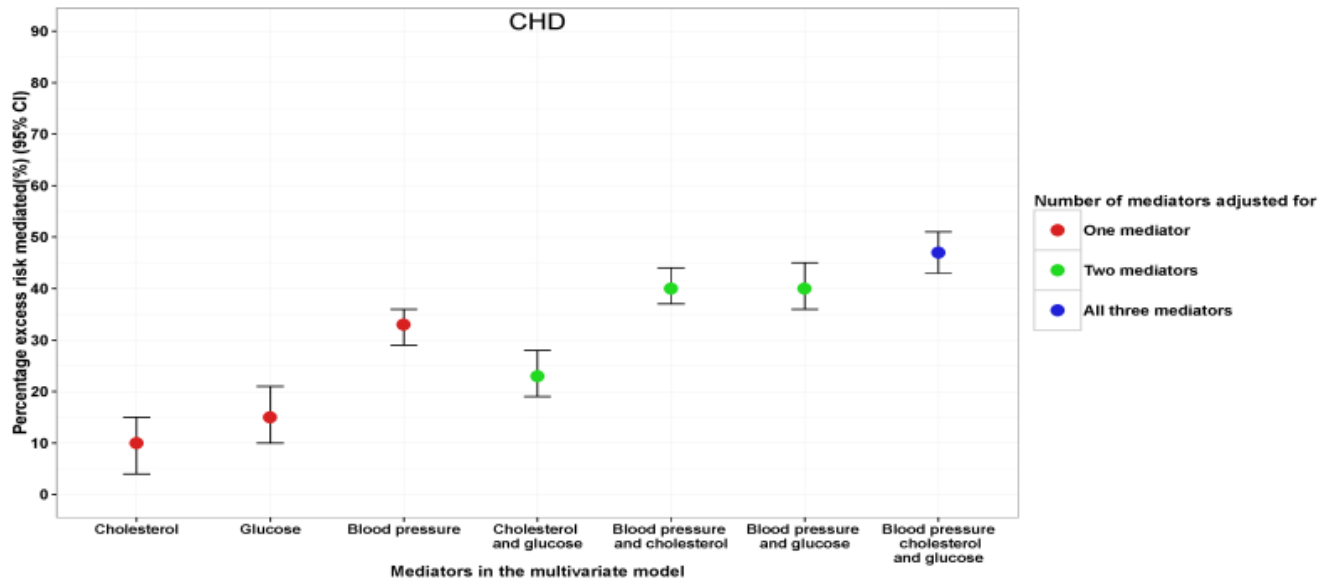Any questions so far?

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RRs per 5 kg/m² BMI adjusted for different combinations of mediators

Percentage of excess risk per 5 kg/m2 BMI mediated by different combinations of mediators

Mediation in overweight versus obesity

	Overweight		Obesity	
	HR (95% CI)	Excess risk mediated (%, 95% CI)	HR (95% CI)	Excess risk mediated (%, 95% CI)
Coronary heart disease				
None	1·26 (1·22 to 1·30)	..	1·69 (1·58 to 1·81)	..
Blood pressure	1·18 (1·14 to 1·22)	31% (26 to 36)	1·48 (1·39 to 1·57)	31% (27 to 35)
Cholesterol	1·21 (1·18 to 1·25)	18% (13 to 22)	1·64 (1·54 to 1·75)	8% (2 to 12)
Blood glucose	1·23 (1·18 to 1·27)	12% (6 to 18)	1·60 (1·49 to 1·72)	14% (8 to 20)
Blood pressure and cholesterol	1·14 (1·11 to 1·18)	45% (40 to 52)	1·44 (1·36 to 1·53)	36% (33 to 40)
Blood pressure and blood glucose	1·16 (1·12 to 1·20)	38% (32 to 45)	1·42 (1·34 to 1·51)	39% (35 to 44)
Cholesterol and blood glucose	1·19 (1·15 to 1·23)	27% (22 to 33)	1·55 (1·46 to 1·64)	21% (17 to 25)
Blood pressure, cholesterol, and blood glucose	1·13 (1·09 to 1·16)	50% (44 to 58)	1·39 (1·32 to 1·47)	44% (41 to 48)

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Sub-group analyses

- Percent Excess Risk Mediated by all 3 mediators for 5 unit higher BMI in different subgroup analyses

	CHD	Stroke
Event type*		
Combined fatal and non-fatal event	50% (46–55)	69% (60–81)
Fatal event	39% (31–49)	115%‡ (78–234‡)
Cohort location†		
North America, western Europe, Australia and New Zealand	44% (40–50)	73% (57–96)
East and southeast Asia	39% (31–49)	79% (59–108‡)
Baseline year		
<1990	53% (46–62)	62% (51–78)
≥1990	38% (34–44)	93% (74–141‡)
Median age at baseline (years)		
<55	45% (41–50)	63% (53–74)
≥55	46% (39–56)	95% (73–149‡)
Follow-up years		
<10	43% (35–52)	89% (67–132‡)
10 to 20	45% (40–52)	84% (68–134‡)
>20	49% (40–59)	52% (44–62)

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Sensitivity analyses

- Using waist circumference or waist-to-hip ratio gave generally similar results to those with BMI.

- LDL cholesterol was a slightly stronger mediator than total cholesterol (5 percentage points in PERM) compared with total cholesterol.

- Cohorts that analyzed self-reported diabetes had slightly higher PERM (3 percentage points PERM) compared with FPG.

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Strengths, limitations and conclusion

Strengths:

- Largest pooling analysis of multiple major CVD risk factors.
- Quantified the role of all possible combinations of three mediators.
- Conducted extensive sub-group analyses.

Limitations:

- Effect sizes of BMI may be affected by unmeasured confounding.
- Did not allow for an interaction between BMI and mediators.
- Stroke subtypes were not analyzed separately due to limited data.

Conclusion

- Interventions that reduce high blood pressure, cholesterol, and glucose may be used to address about one half of excess risk of CHD and three quarters of excess risk stroke associated with overweight/obesity

Clinical example

- Consider a 70-year-old, non-smoking man who does not have diabetes, is 174 cm tall and weighs 100 kg (i.e., has a BMI of 33 kg/m2), with a SBP of 147 mm Hg, total cholesterol of 5.05 mmol/L, and HDL cholesterol of 0.93 mmol/L.

- Framingham risk score estimate of 10-year risk of CHD for this man is 25%

- If he would lose 15kg of weight (i.e. 5 units of BMI), his new risk would be 20%

- If he could control his SBP and cholesterol to levels corresponding to 15kg weight loss, his new risk would be 23%

Global impact of risk factors on mortality

Danaei et al – forthcoming
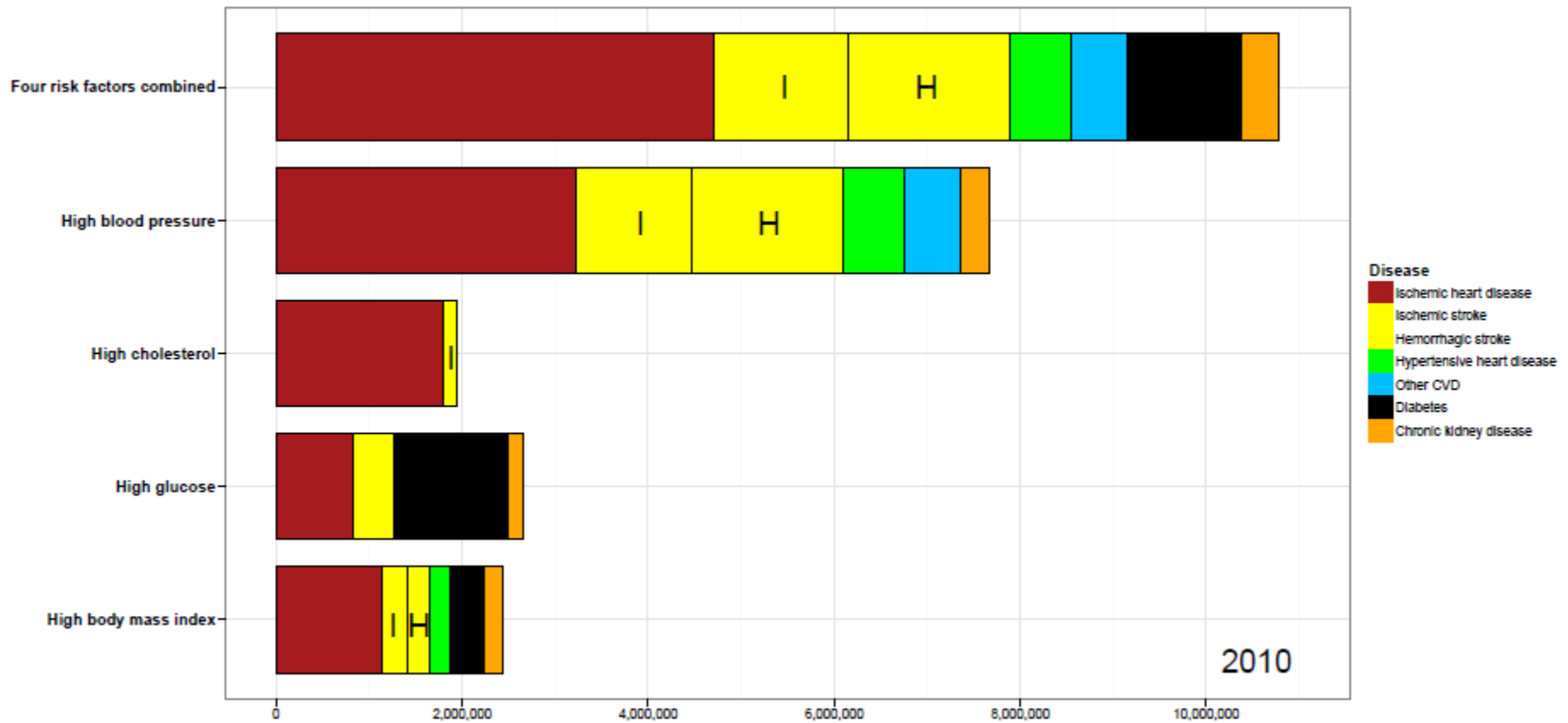
Co-authors and Acknowledgements

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Questions ?