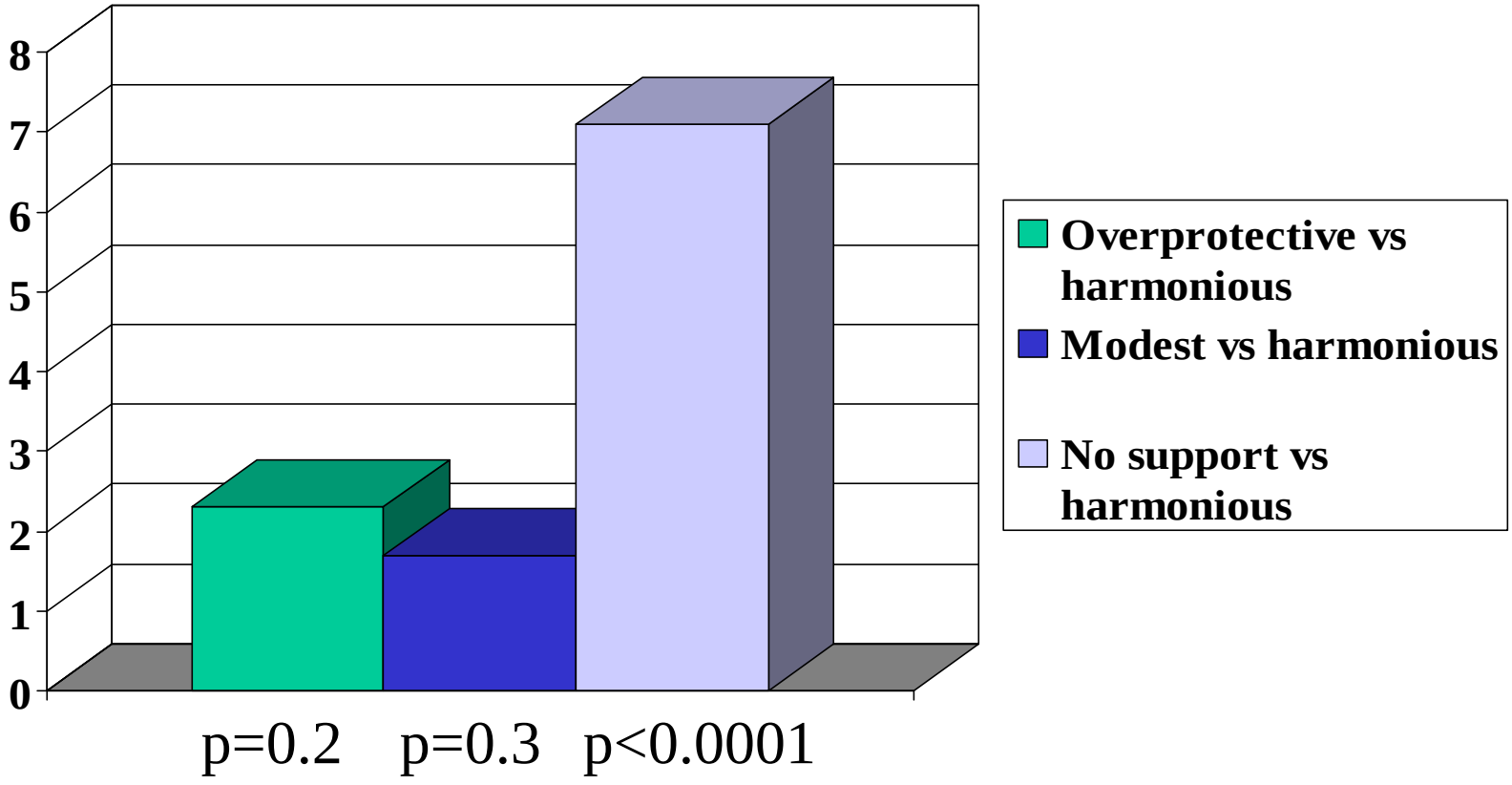
Parental neglect during childhood and increased risk of obesity in young adulthood

Inge Lissau, Thorkild I A Sørensen

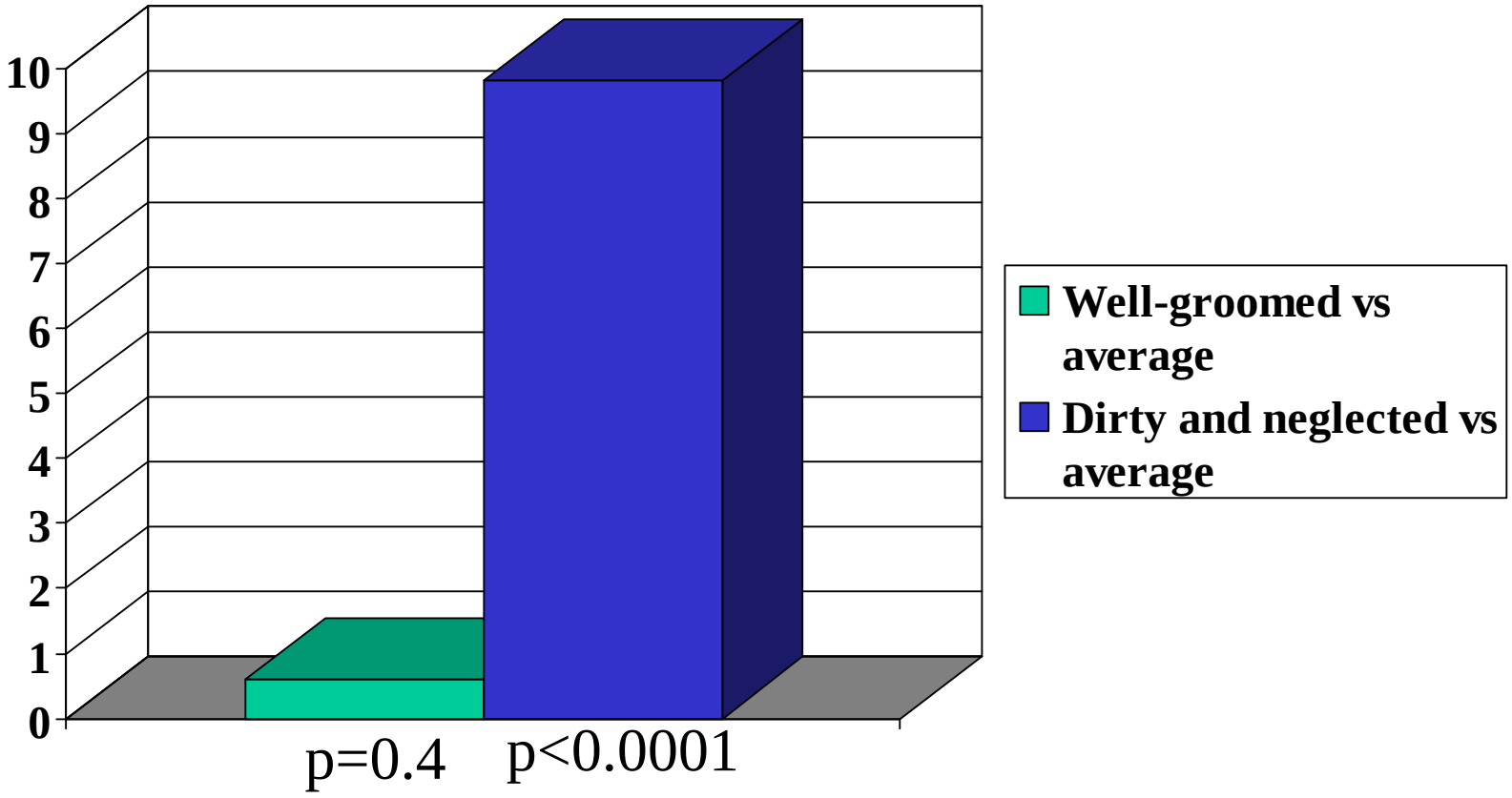
Odds ratio for obesity by parental support perceived by the teacher



Parental neglect during childhood and increased risk of obesity in young adulthood

Inge Lissau, Thorkild I A Sørensen

Odds ratio for obesity by appearance at school health exa



The excess food intake

- The hypothesis that observable excess food intake is the driver of the epidemic must be based on an expectation that the tiny surplus in ES is a consequence of excessive load breaking the counterregulatory system that in this case is also needed to explain why ES is so tiny.
- Generally, multiple studies of observable or induced individual differences in food intake and physical activity have been unable to show unequivocal associations with subsequent obesity development from the non-obese state.

Systematic literature review

- Summerbell et al recently published a systematic review of the available literature on general population-based prospective investigations of the associations between foods and subsequent weight gain and obesity in International Journal of Obesity (2009;33:S13-S27)

Key findings in the review

- Several, large-scale, prospective, long-term general population-based observational epidemiological studies have addressed the question.
- They provide no convicing evidence for any association of any specific food (or total energy intake) with risk of excessive weight gain and eventual development of obesity in children, adolescents, and adults.

Is this really the truth?

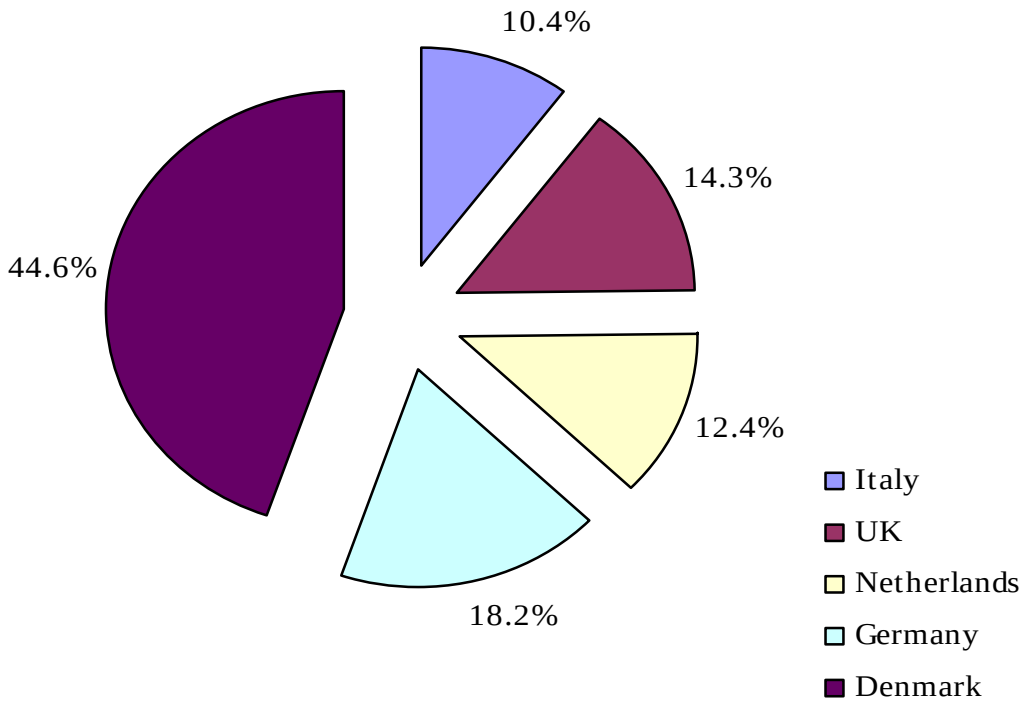
- Could there still be important effects of diet on weight gain and risk of obesity that these studies have been unable to unravel?
- Could the well known methodological problems in this sort of epidemiology and specifically in nutritional epidemiology have hidden the true associations?

The DIOGENES project

- A large EU FP6 IP project, DIOGENES (Diet, Obesity and Genes) running from 2005 through 2009 may contribute
- Primarily focused on the role of proteins and glycemic index in prevention of weight gain in the general population and re-gain after weight loss among obese individuals, but included additional food context, e.g. F&V

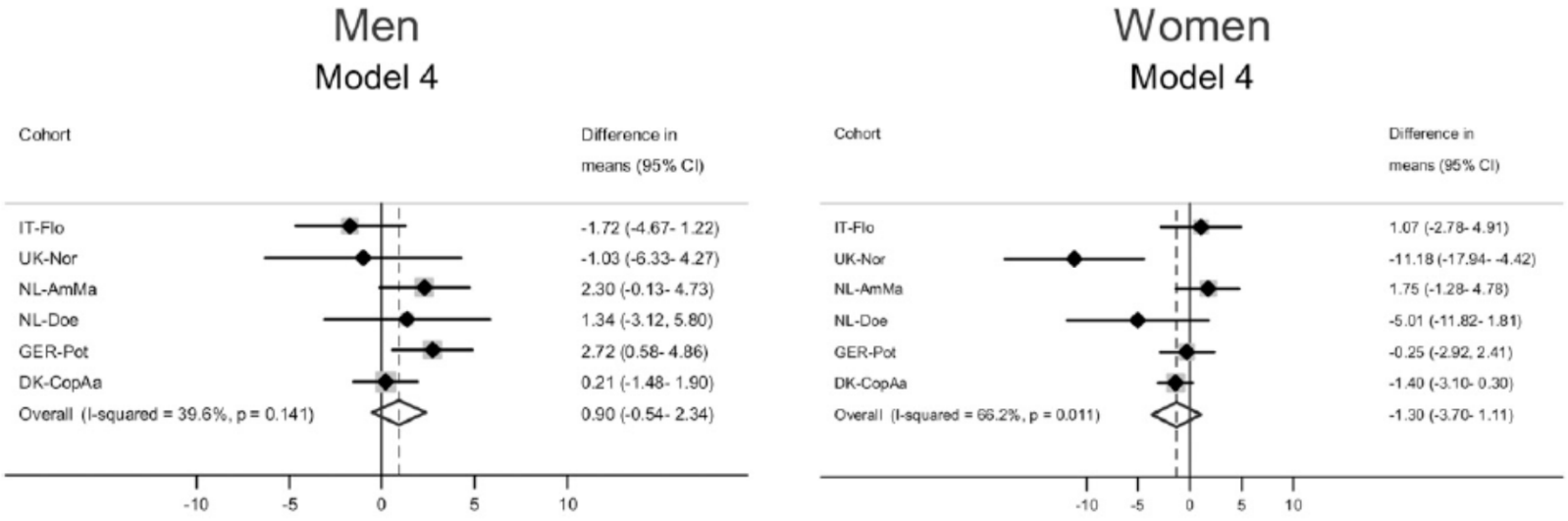
DiOGenes study

EPIC-based studies in DiOGenes



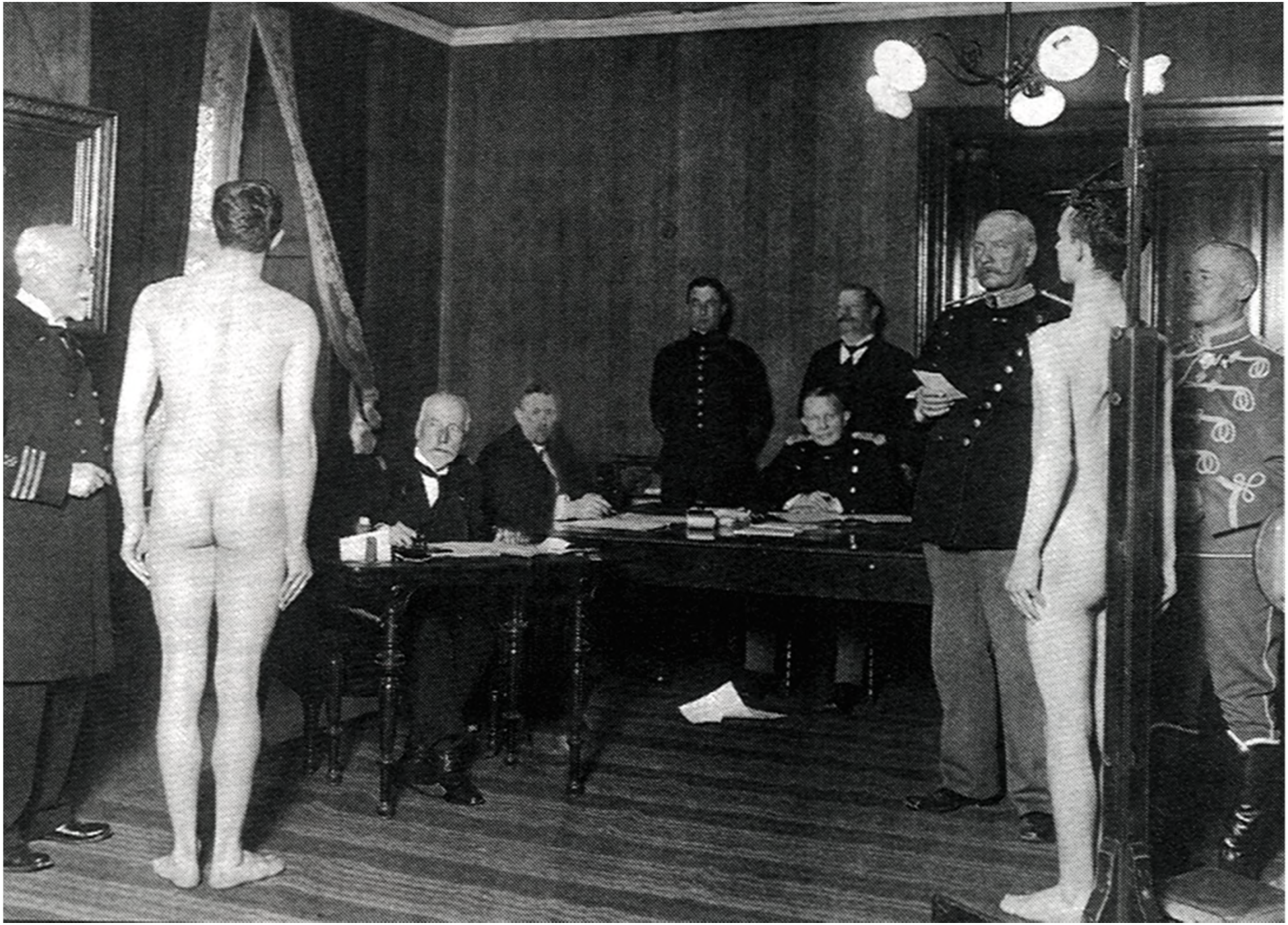
- 89,432; 41.5% men
- Baseline age: 53 (20 - 78) yrs
- Mean follow-up time: 6.5 (1.9 - 12.5) yrs

Association between dietary fat intake and annual weight change determined by the residual method in which energy-adjusted fat intake was the exposure and total energy intake was a covariate in the model: DiOGenes

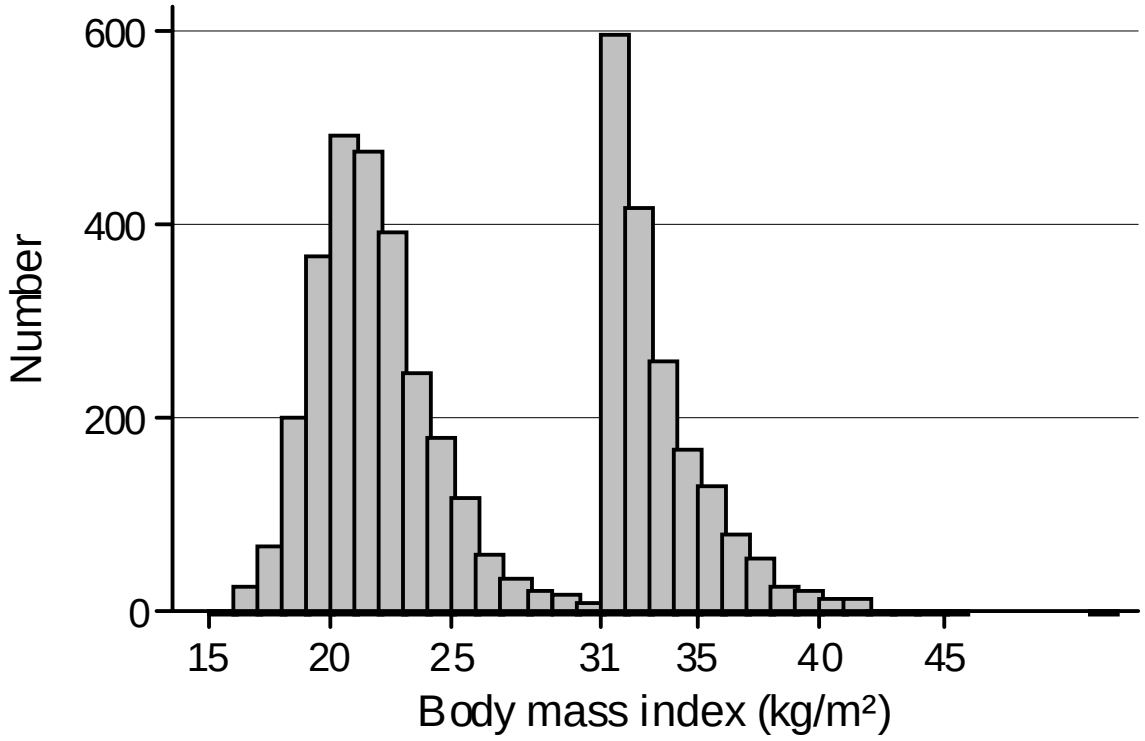


Model 4: Analyses adjusted for baseline age, baseline weight, baseline height, total energy intake, duration of follow-up, baseline smoking status, follow-up smoking status, baseline physical activity, highest school level, menopausal status, hormone use for menopause at baseline, alcohol (g), protein intake (as % of total energy intake)

Am J Clin Nutr 2009;90:1632–41

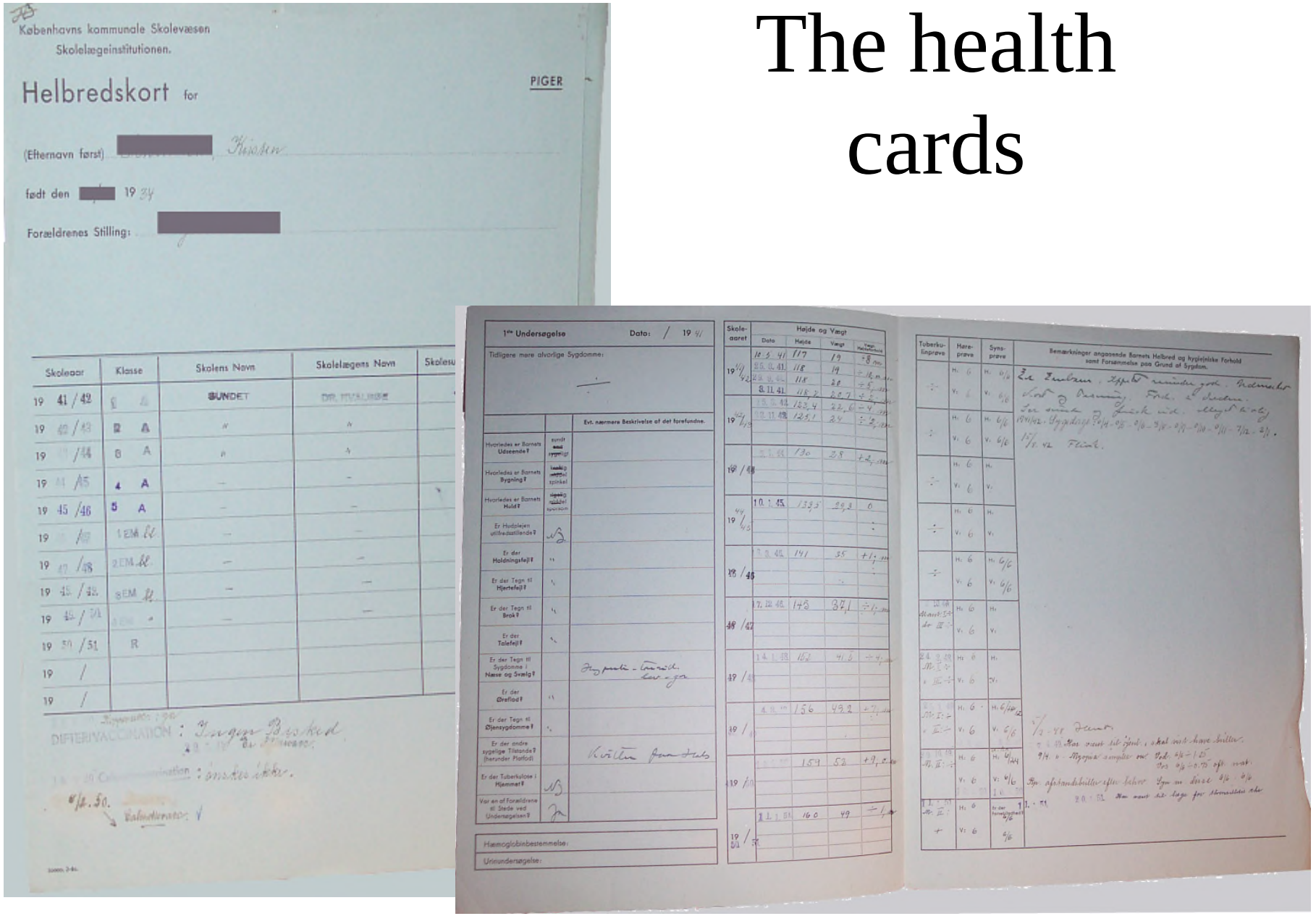


Distribution of BMI at draft board examination for 3601 men sampled randomly as 1% of all 360,000 men and all 1930 men with BMI $\geq$ 31 kg/m2



The records

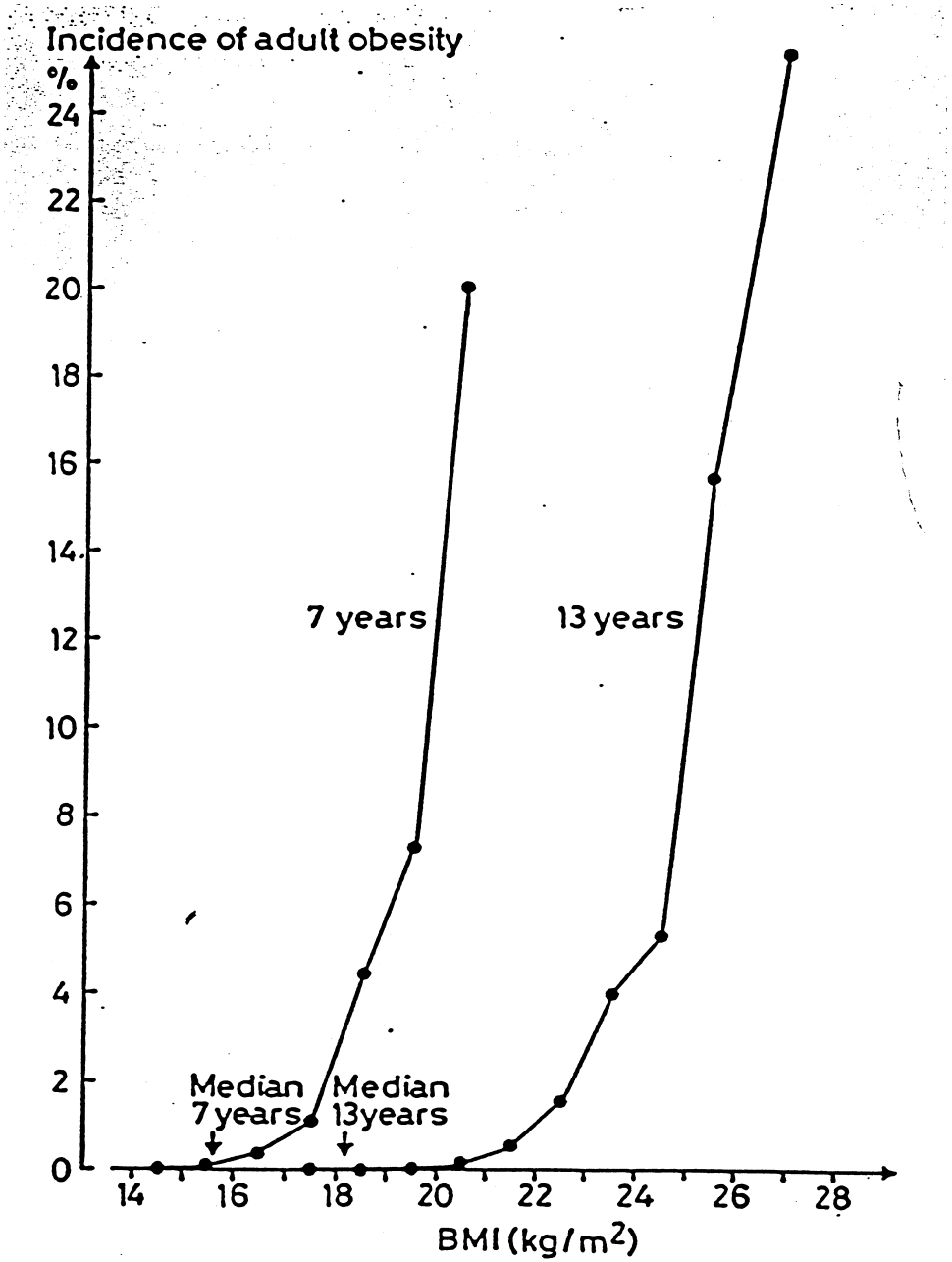
The health cards



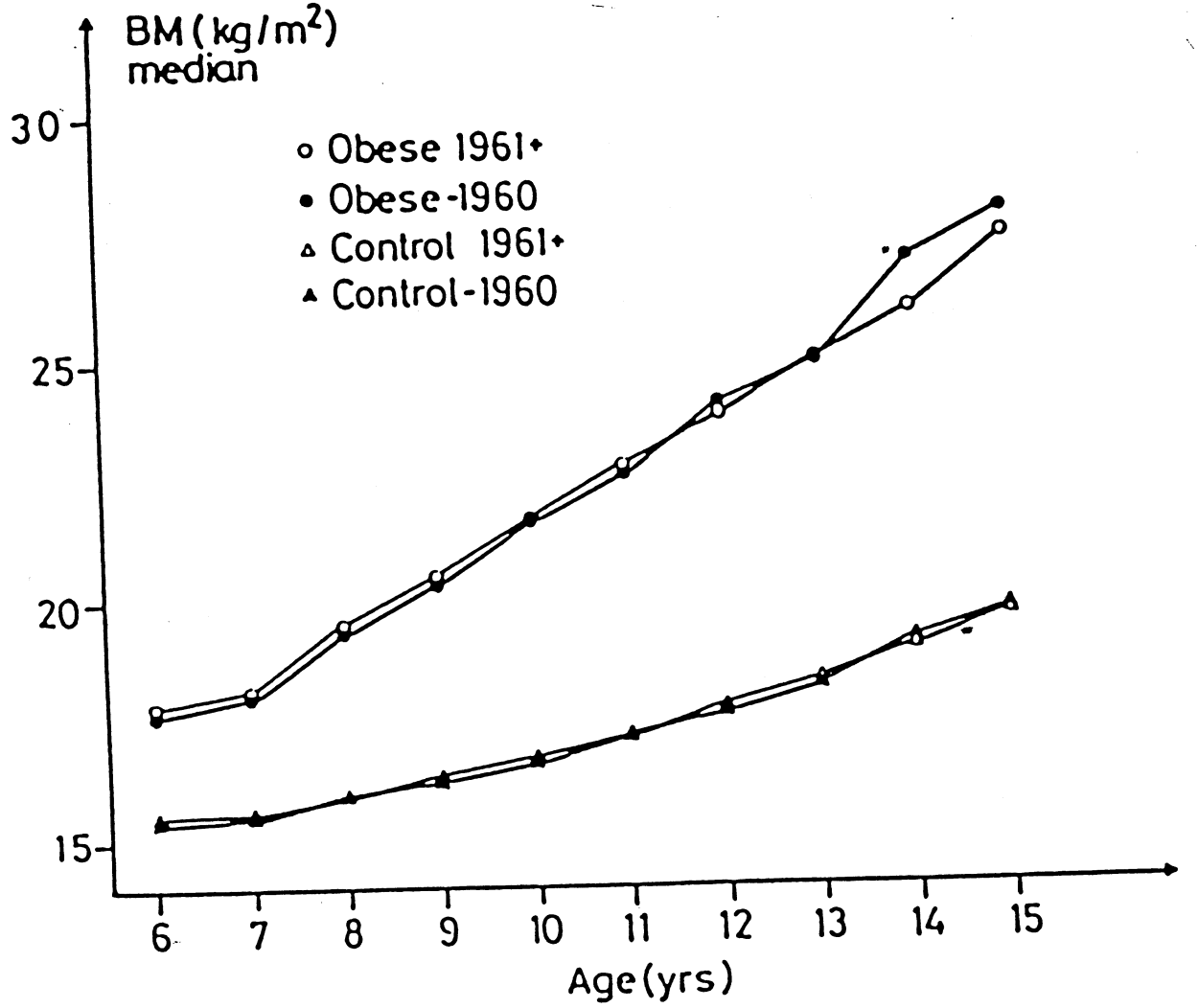
Study of school children

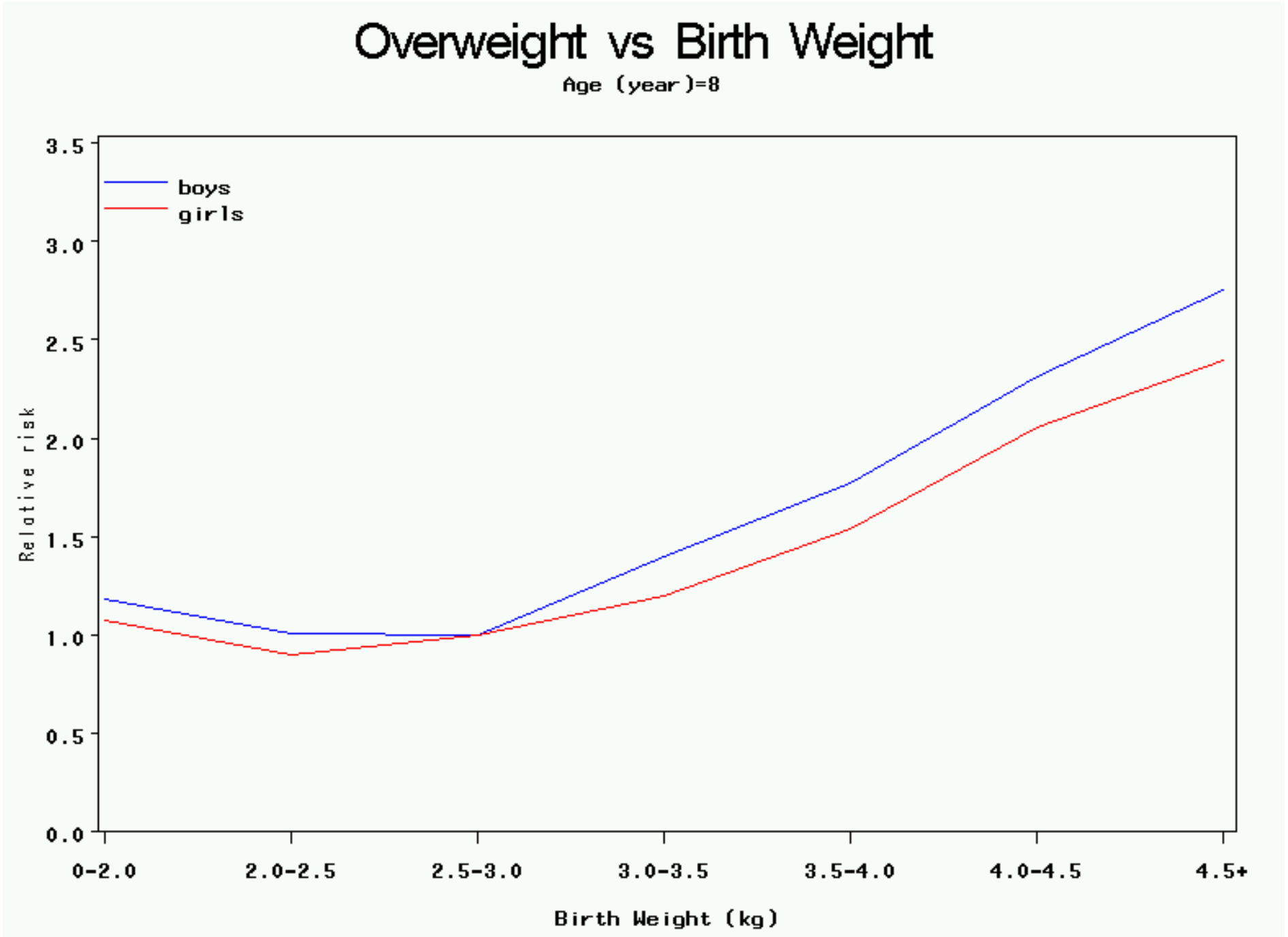
- School health records may give part of the answer to the questions about the history.
- From 1936, all school children in Copenhagen municipality have had mandatory health exams, annually until 1983, at start and end of schooling thereafter
  - In public and private schools
  - Weight and height were recorded on health cards
  - Parents reported birth weight at the 1st exam.

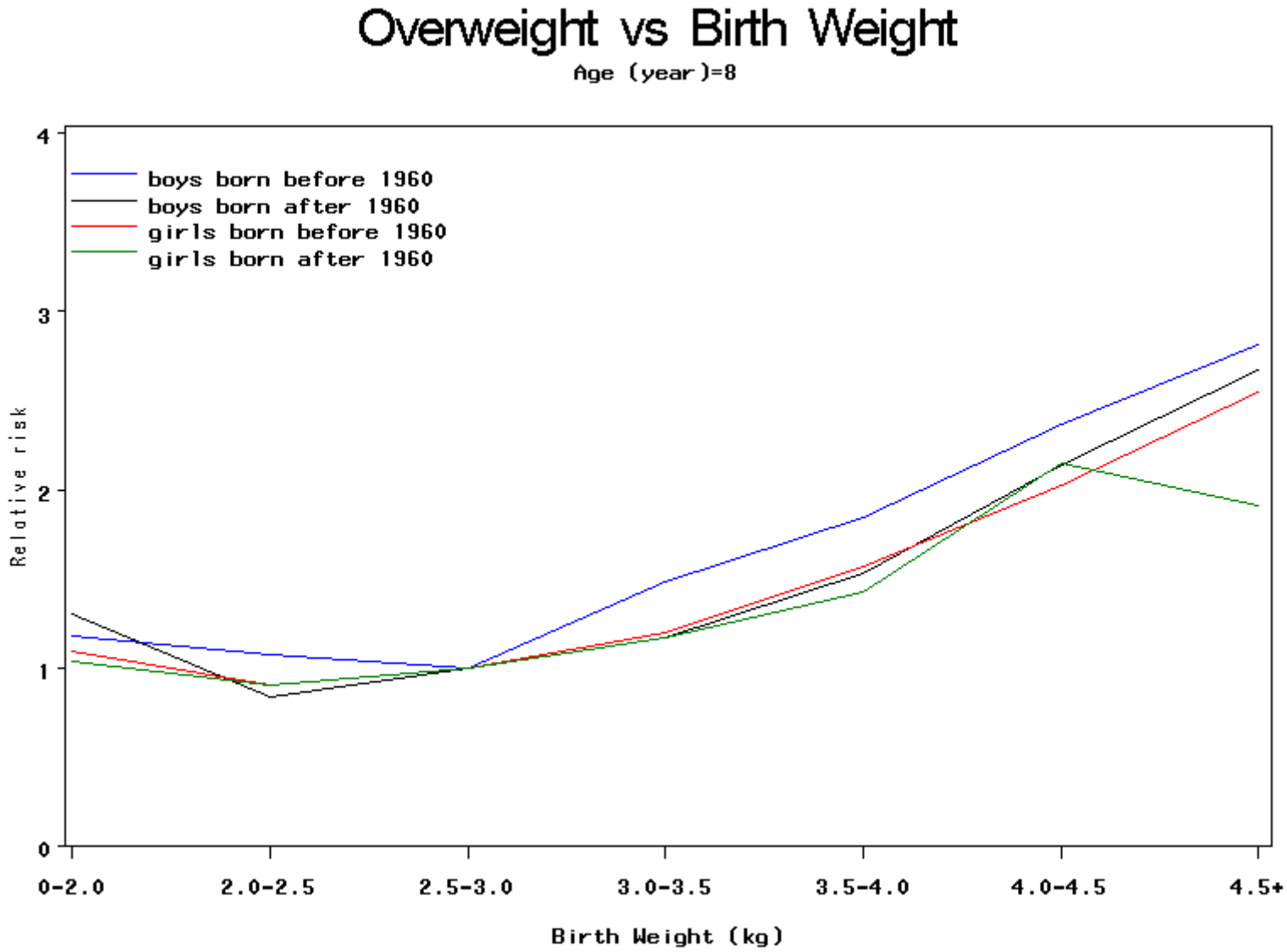
Birth cohorts	Draftees (18-23y)		Boys (6-8y)		Birth weights
Year	Total	Obese	Total	Obese	Total
1930-33	35159	47	12776	18	0
1934-38	45092	54	20988	20	8772
1939-43	52154	94	25082	43	21728
1944-48	81849	413	27680	52	25674
1949-53	96664	692	21480	67	19695
1954-58	80643	736	15271	55	13976
1959-63	62734	513	9186	32	8464
1964-68	86953	698	10259	44	9445
1969-73	76830	862	8052	49	7270
1974-78	66987	1516	7039	67	6203
1979-83	23277*	742*	6022	81	5164
Total	708342	6367	163835	528	126391


Incidence of adult obesity
%
24
22
20
18
16
14
12
10
8
6
4
2
0
7 years
13 years
Median 7 years
Median 13 years
14
16
18
20
22
24
26
28
BMI (kg/m2)

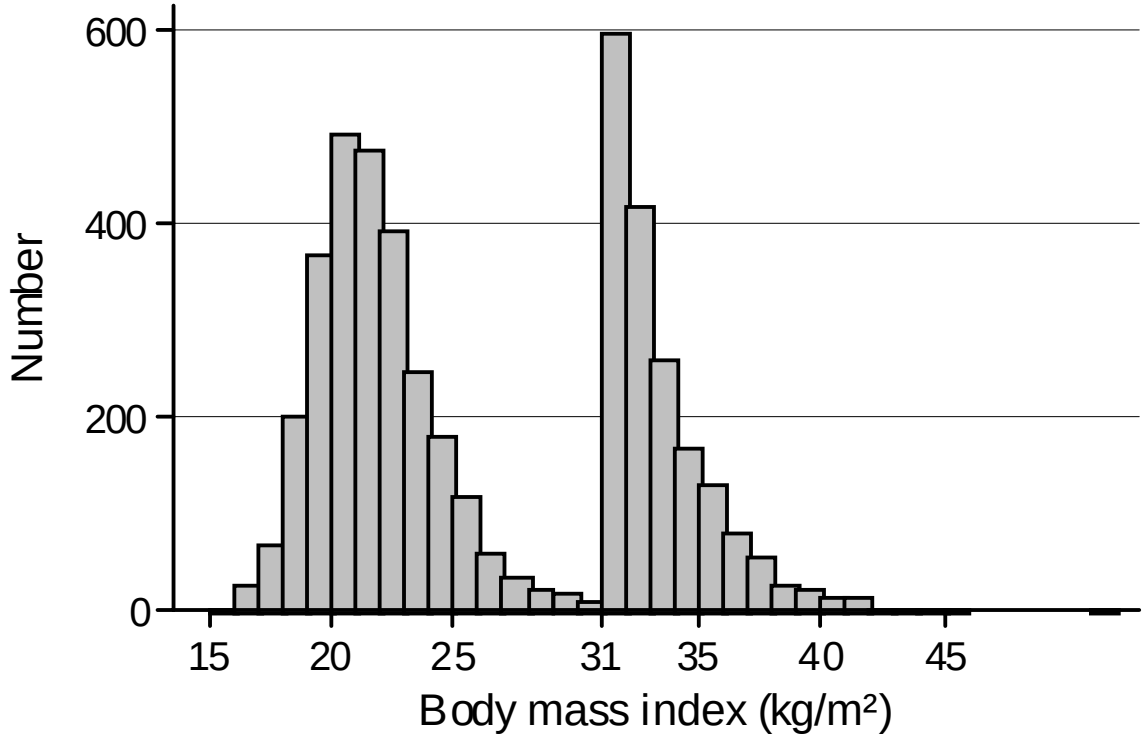
Case-control nested in cohort study (designed as a case-cohort study) of childhood BMI in relation to be obese at draft board examination




Overweight vs Birth Weight
Age (year)=8
boys
girls
Relative risk
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0-2.0
2.0-2.5
2.5-3.0
3.0-3.5
3.5-4.0
4.0-4.5
4.5+
Birth Weight (kg)

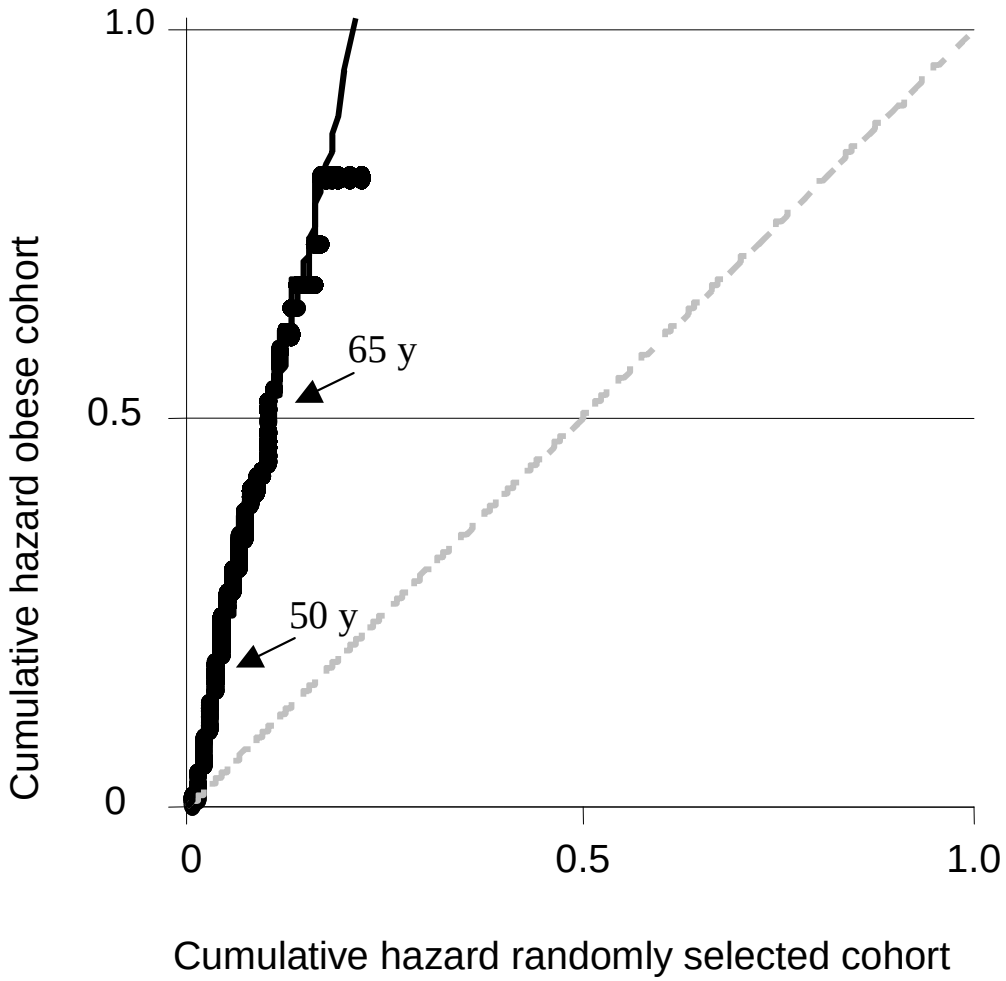

Overweight vs Birth Weight
Age (year)=8
boys born before 1960
boys born after 1960
girls born before 1960
girls born after 1960
Relative risk
0
1
2
3
4
0-2.0
2.0-2.5
2.5-3.0
3.0-3.5
3.5-4.0
4.0-4.5
4.5+
Birth Weight (kg)

Distribution of BMI at draft board examinations 1943-1977 for all 1930 men with BMI ≥ 31 kg/m2 among 360,000 men compared with 3601 men sampled at random as 1% of all

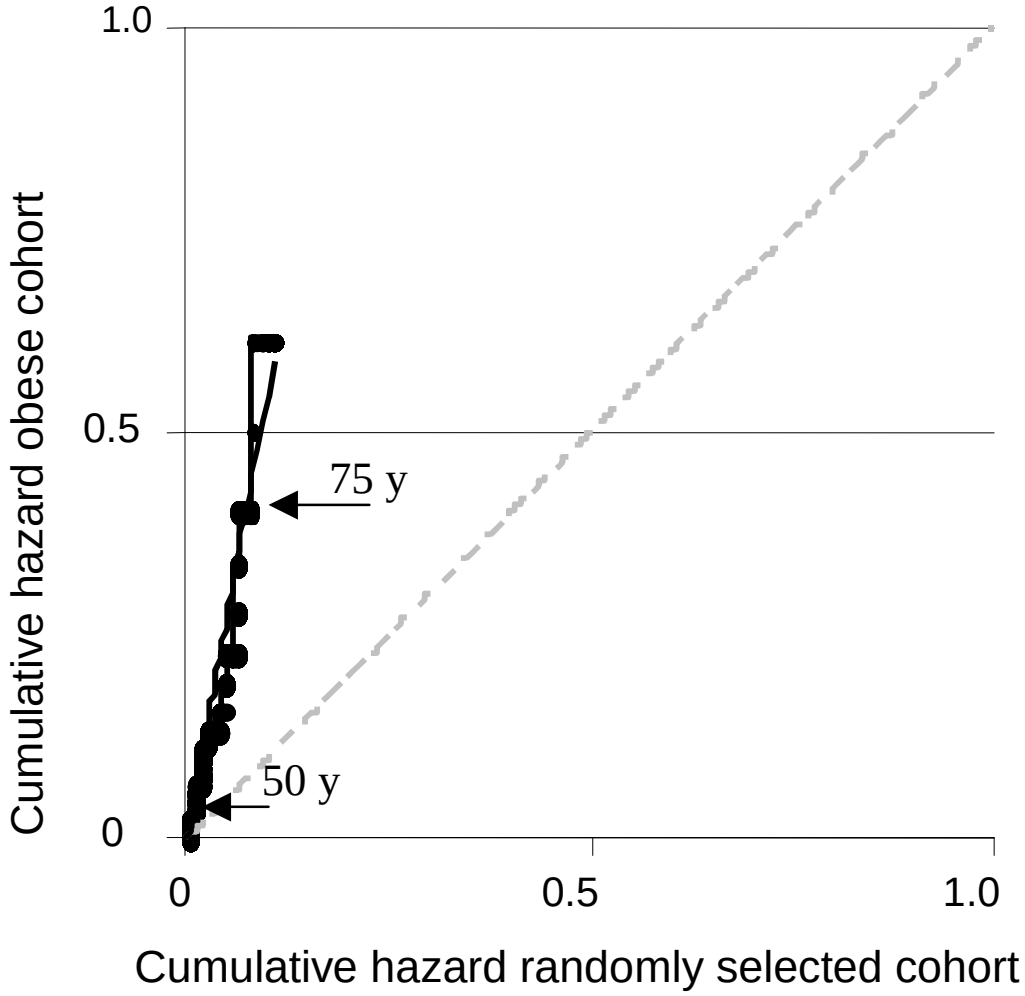


Cause-specific morbidity and mortality in the obese men versus the randomly selected Danish young men throughout their lives

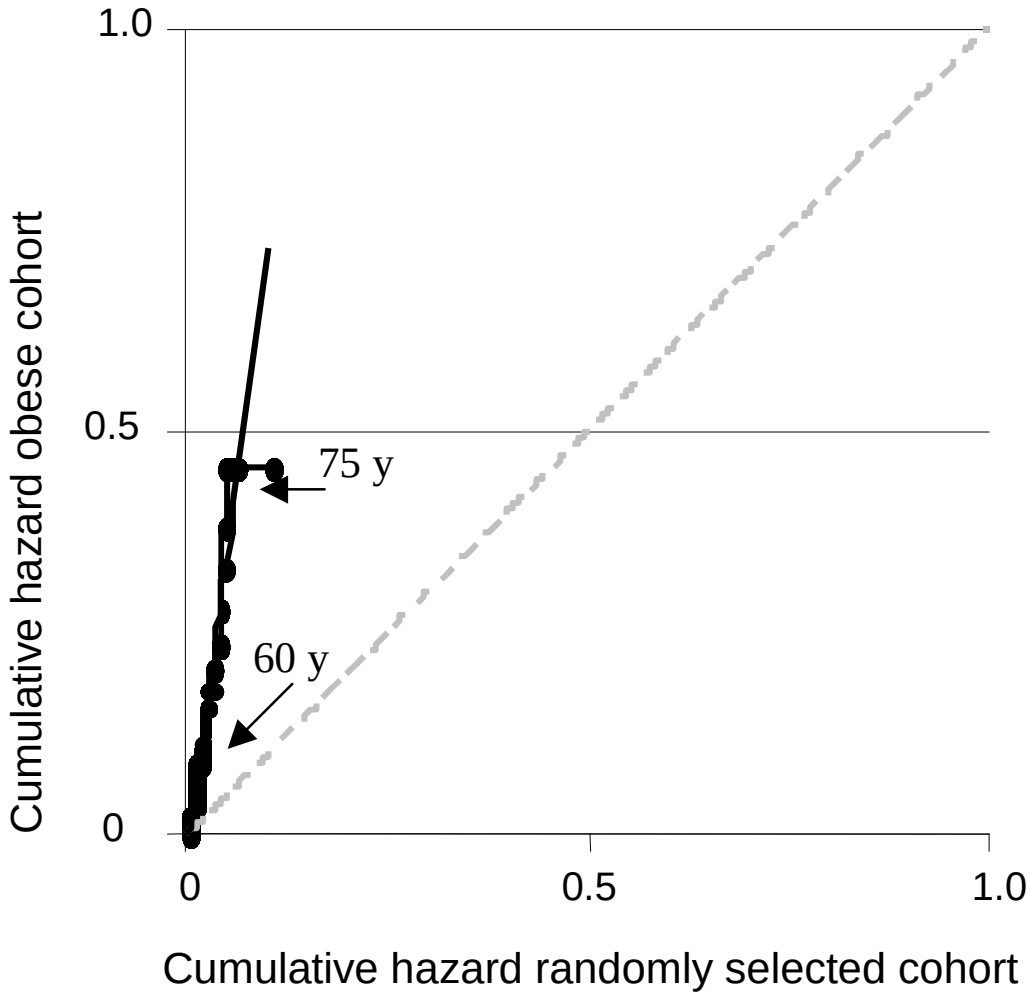
Incidence of diabetes: RR 4.92 (4.14-5.85)



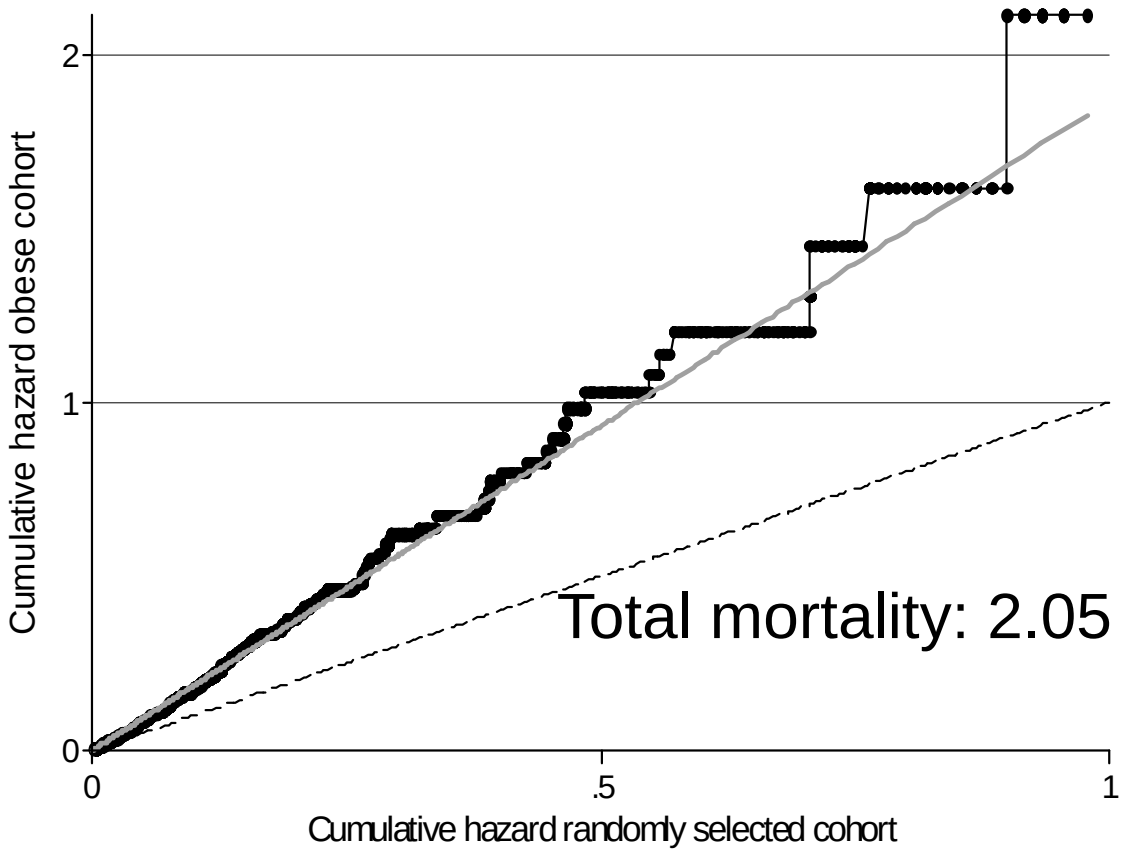
Diabetes in the year preceding death RR 5.23 (3.63-7.54)



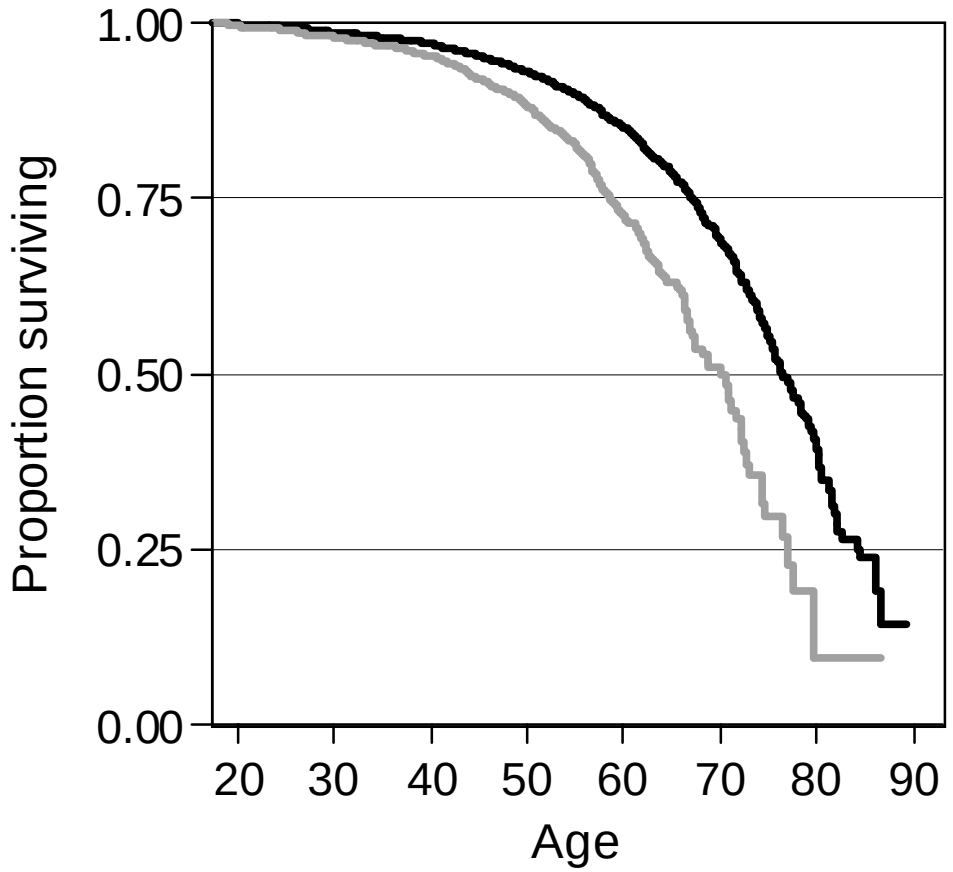
Prevalent diabetes at death RR 6.83 (4.62-10.09)



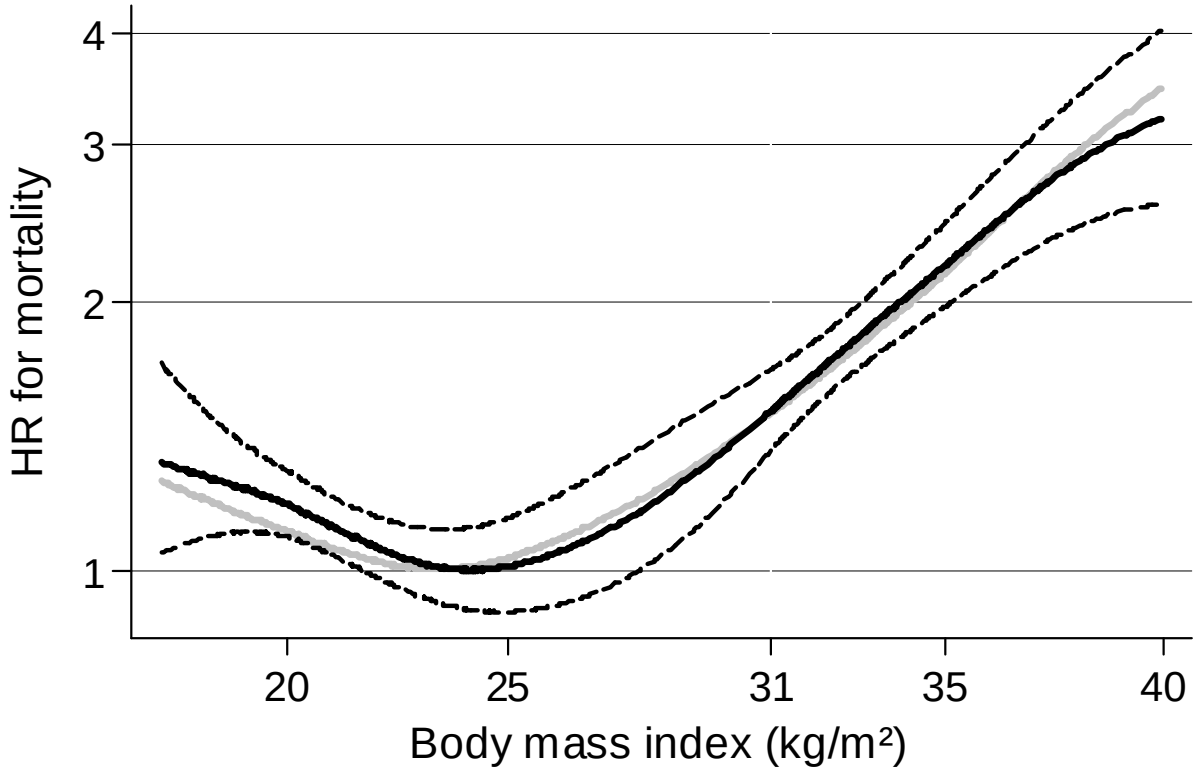
Cumulative hazard plot of total mortality of the obese cohort versus the randomly selected cohort



Kaplan Meier plots for the obese cohort (grey line) and the randomly selected cohort (black line)



BMI at draft board examination and all-cause mortality (smoothing splines)

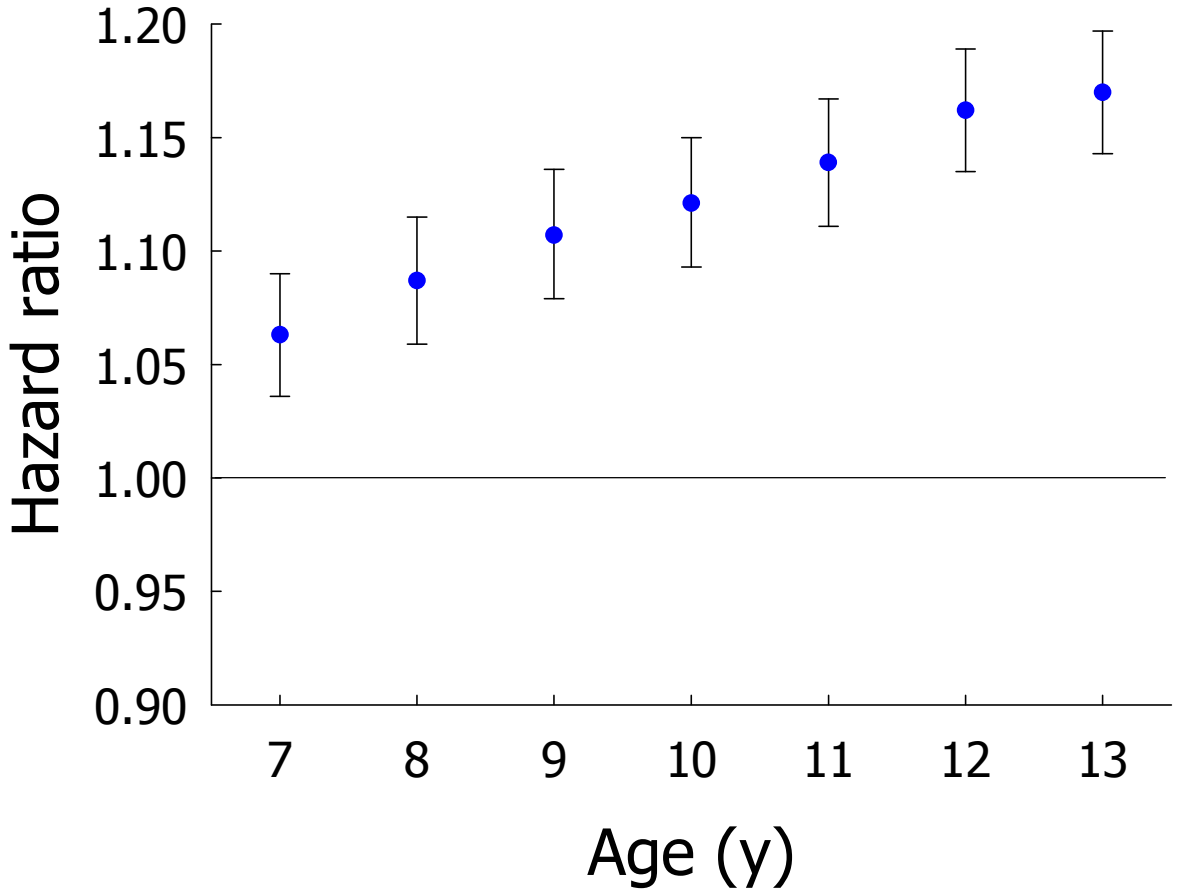


The records

CHD events

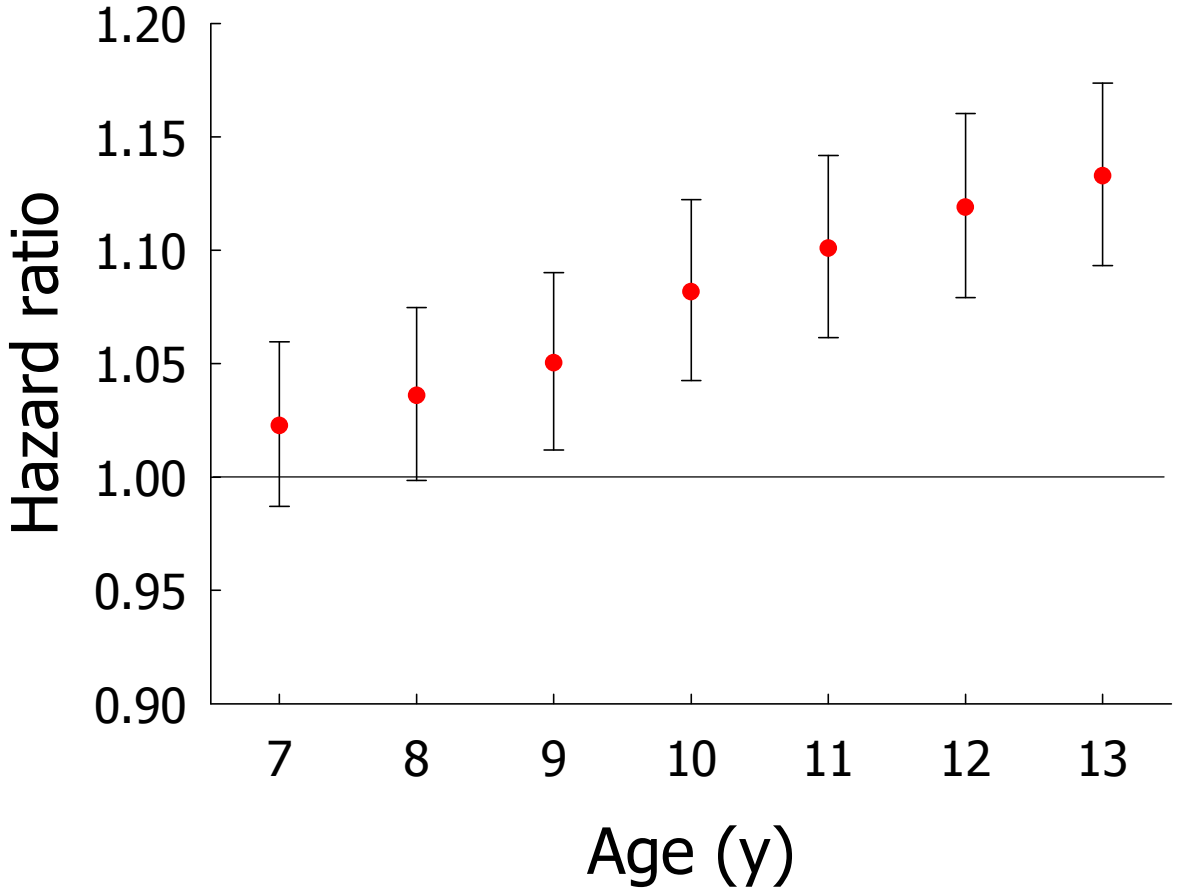
	CHD event		
Subjects	Yes	No	Person-years of follow-up
Boys	9,892	125,960	2,438,175
Girls	3,815	127,789	2,323,272

Association between BMI z-scores at ages 7-13 y and adult CHD among boys



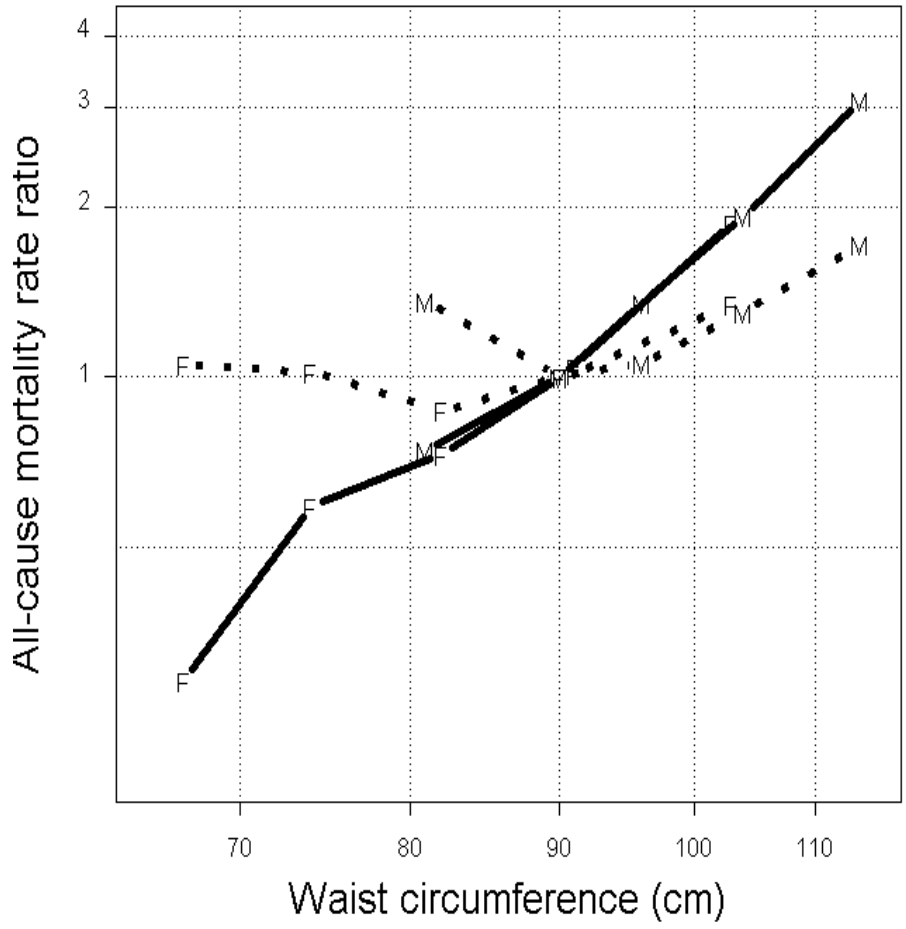
From: Baker et al. *NEJM* 2007:357;2329-2337

Association between BMI z-scores at ages 7-13 y and adult CHD among girls

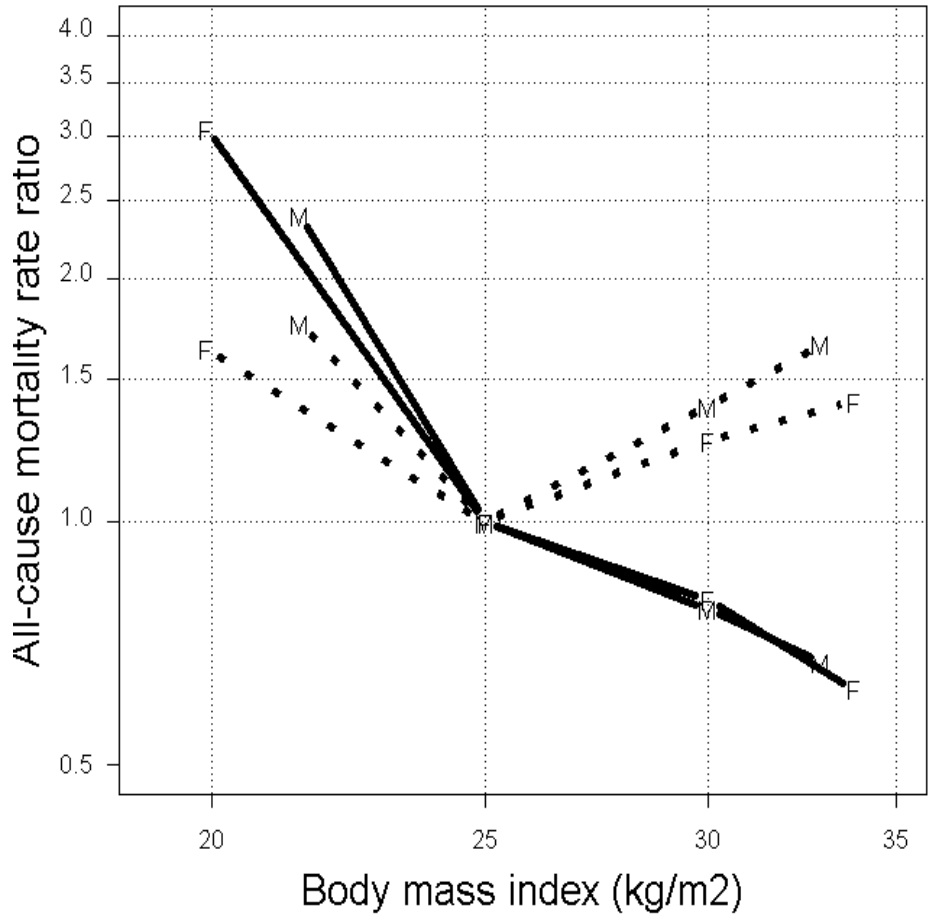


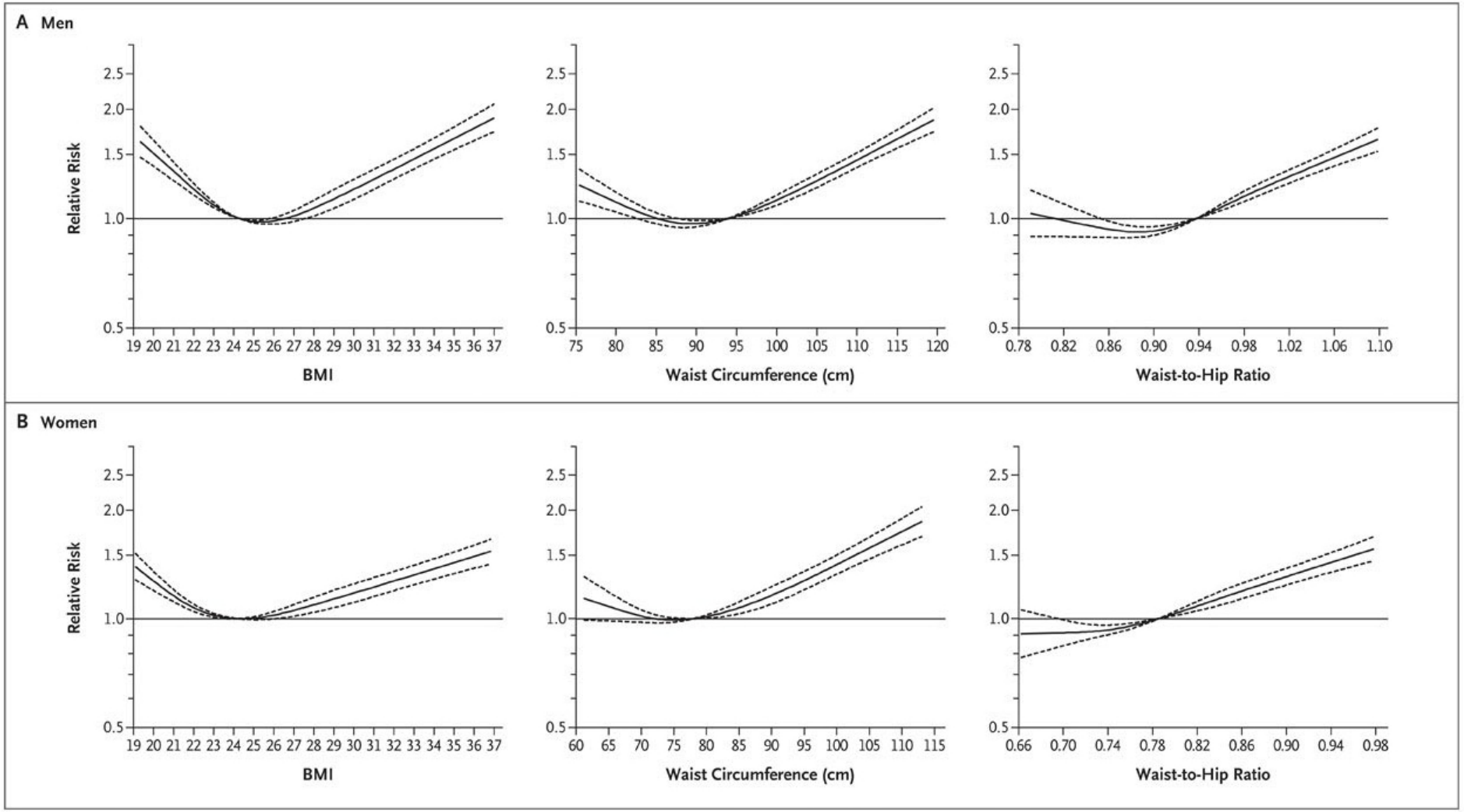
From: Baker et al. *NEJM* 2007:357;2329-2337

Waist circumference, adjusted for BMI, and all-cause mortality assessed in the Danish Diet, Cancer and Health cohort of 57,000 men and women aged 50-64 years at baseline (the Danish EPIC)

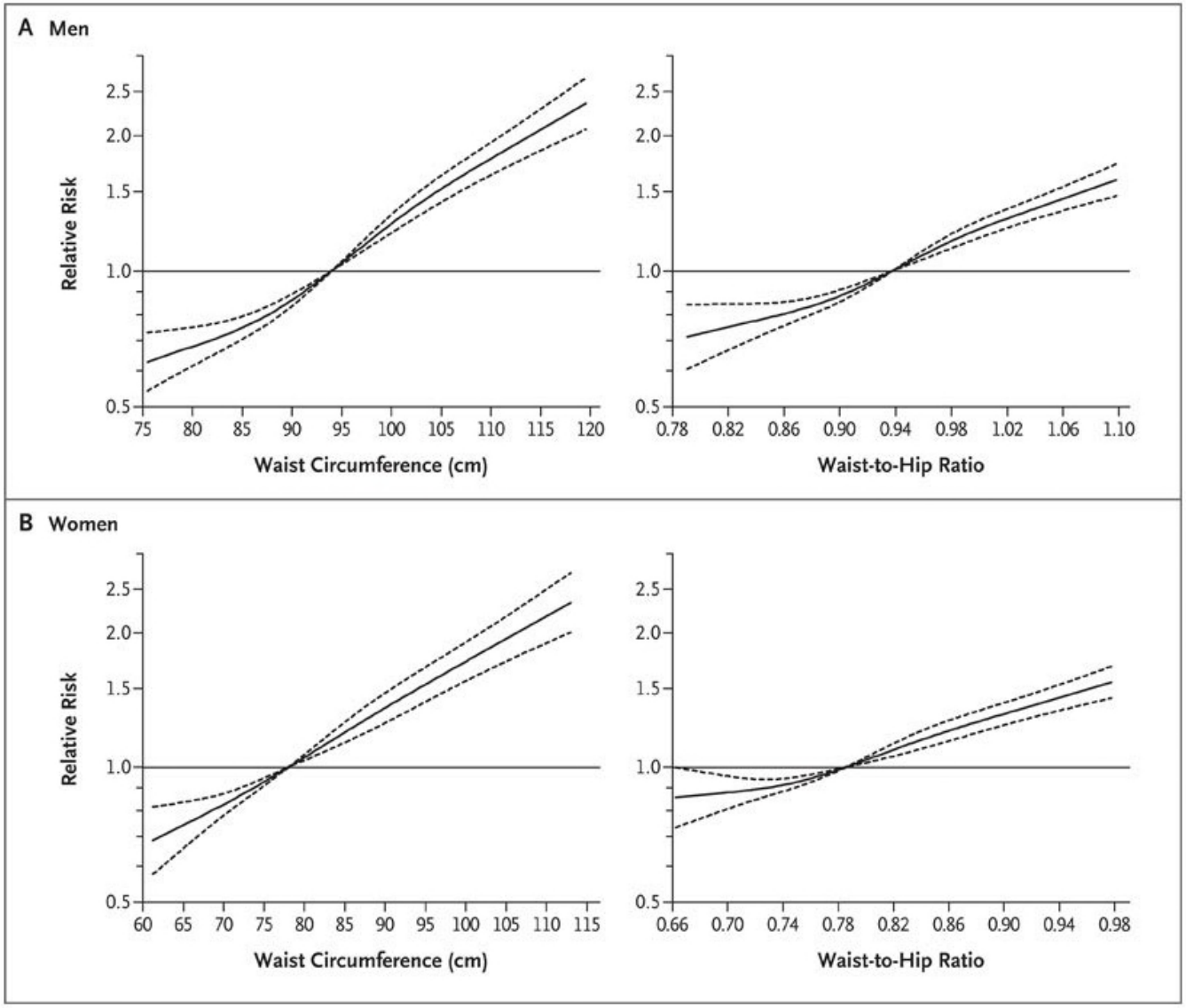


BMI and all-cause mortality

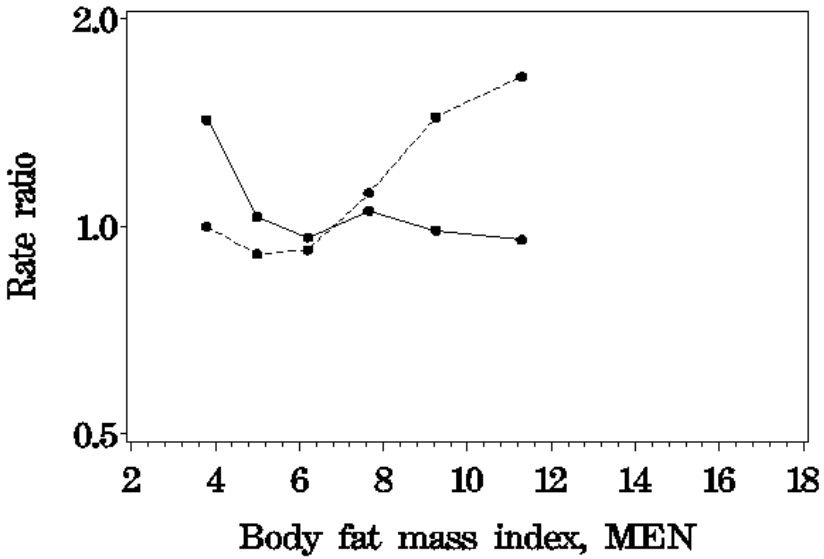


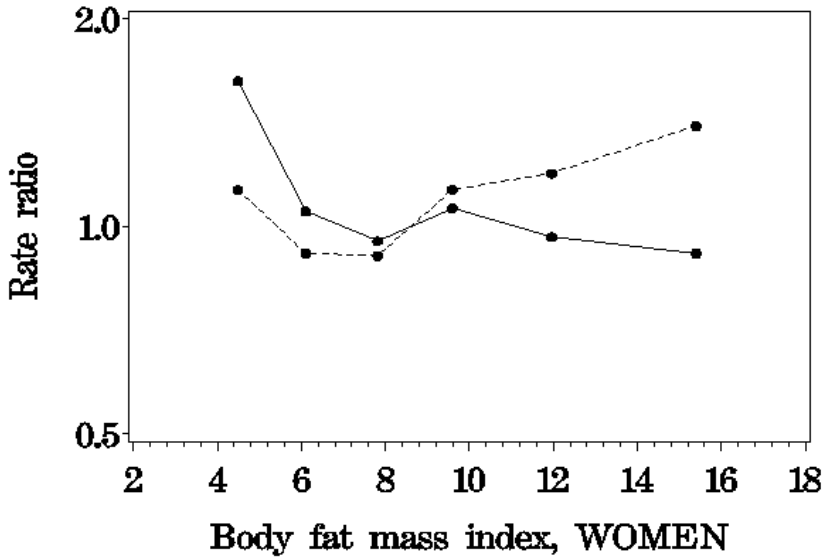


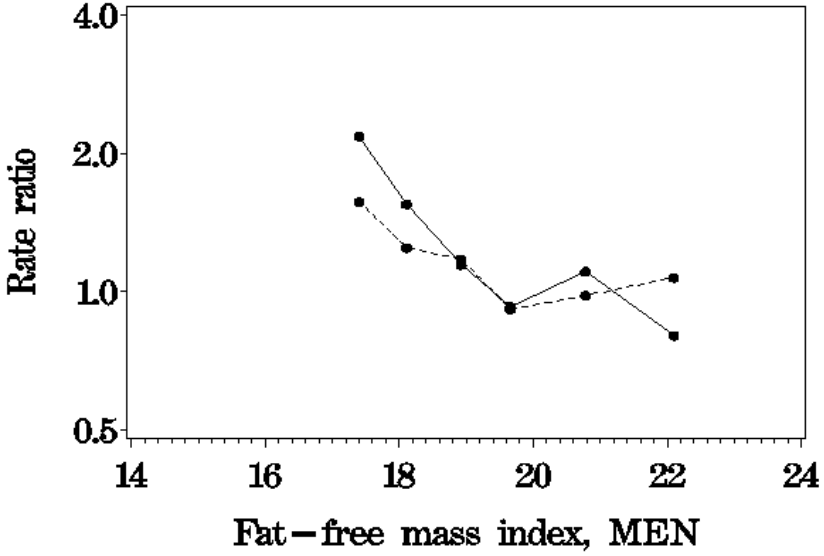
The NEW ENGLAND JOURNAL of MEDICINE

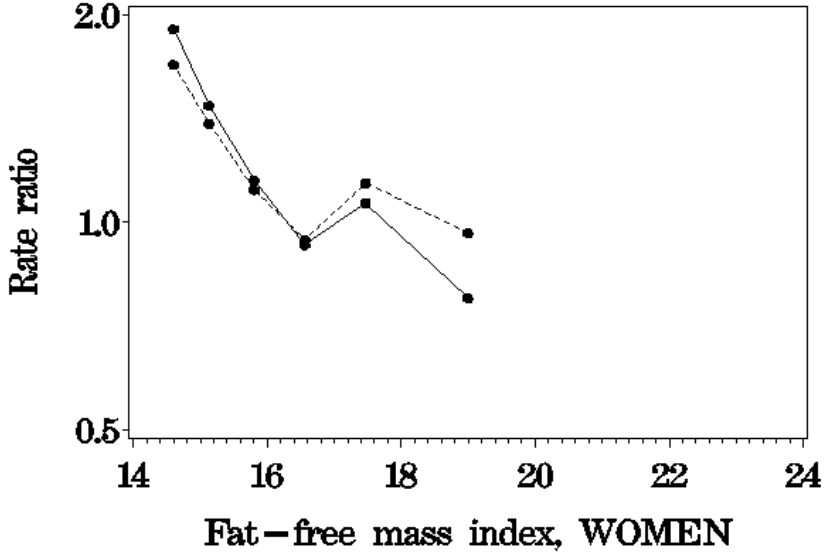


Body composition, waist circumference, and mortality in men and women aged 50-64 Yrs





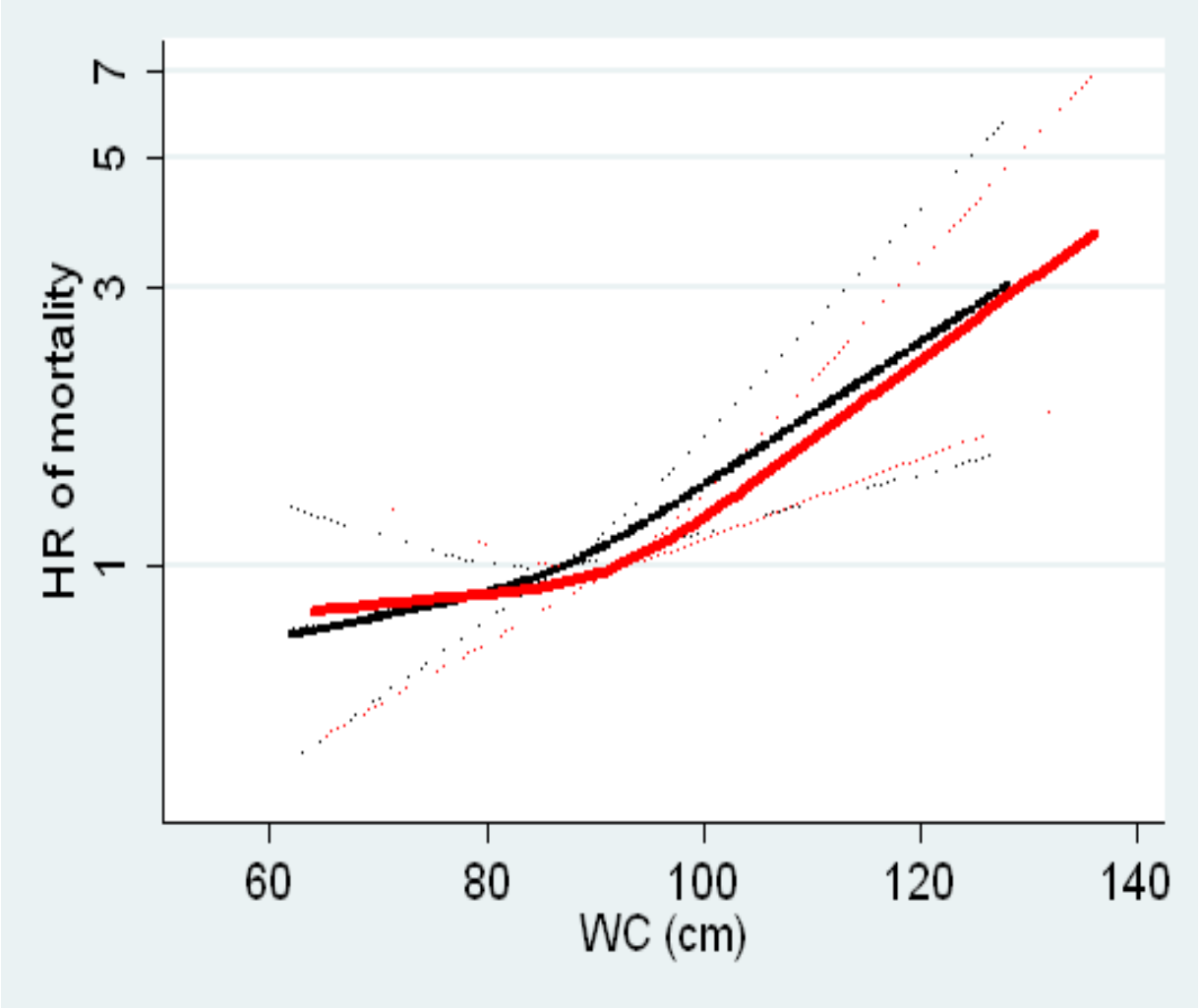


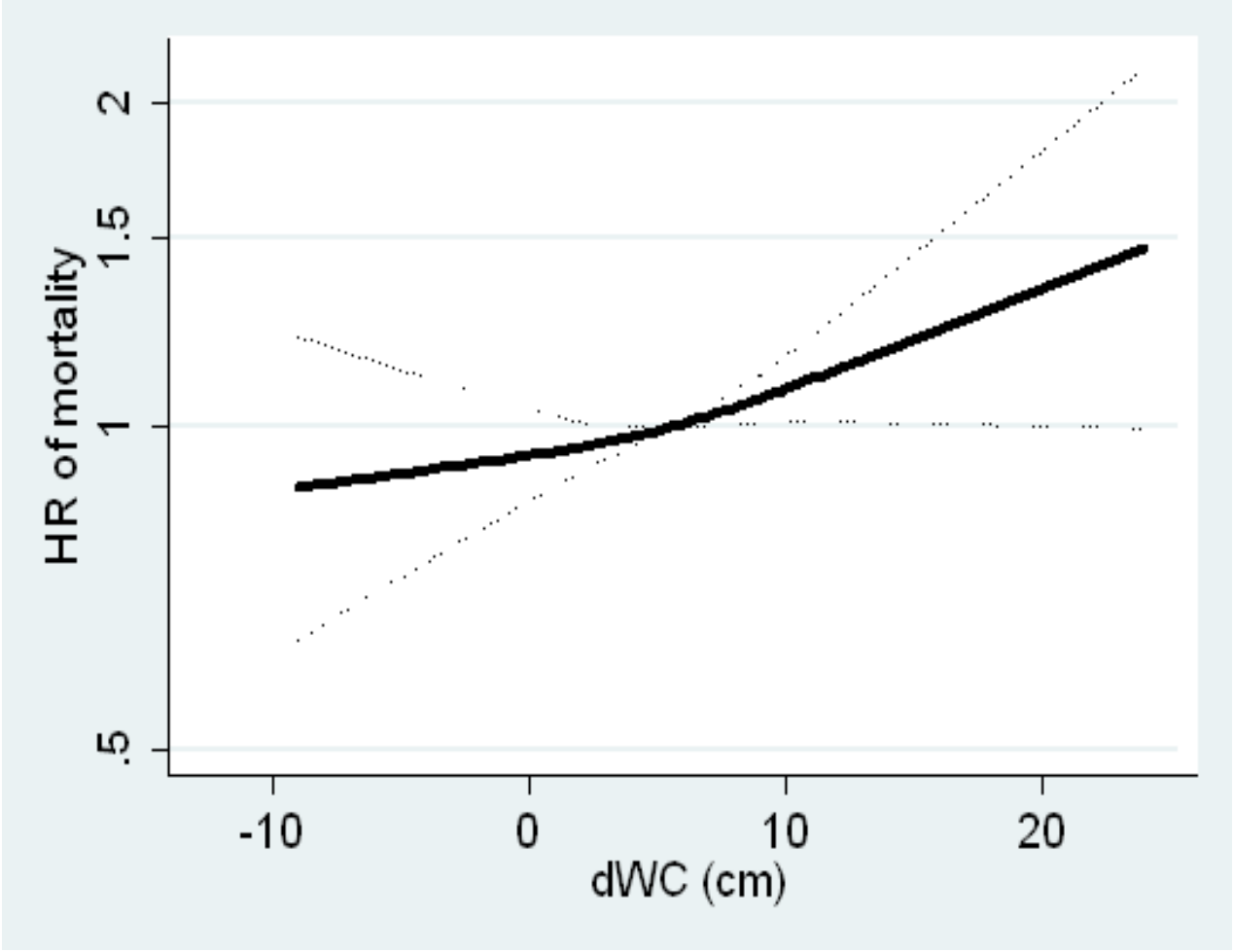


This series of studies – supported by other studies – strongly suggest that the body compartments have different impact on health, even measured crudely as total mortality:

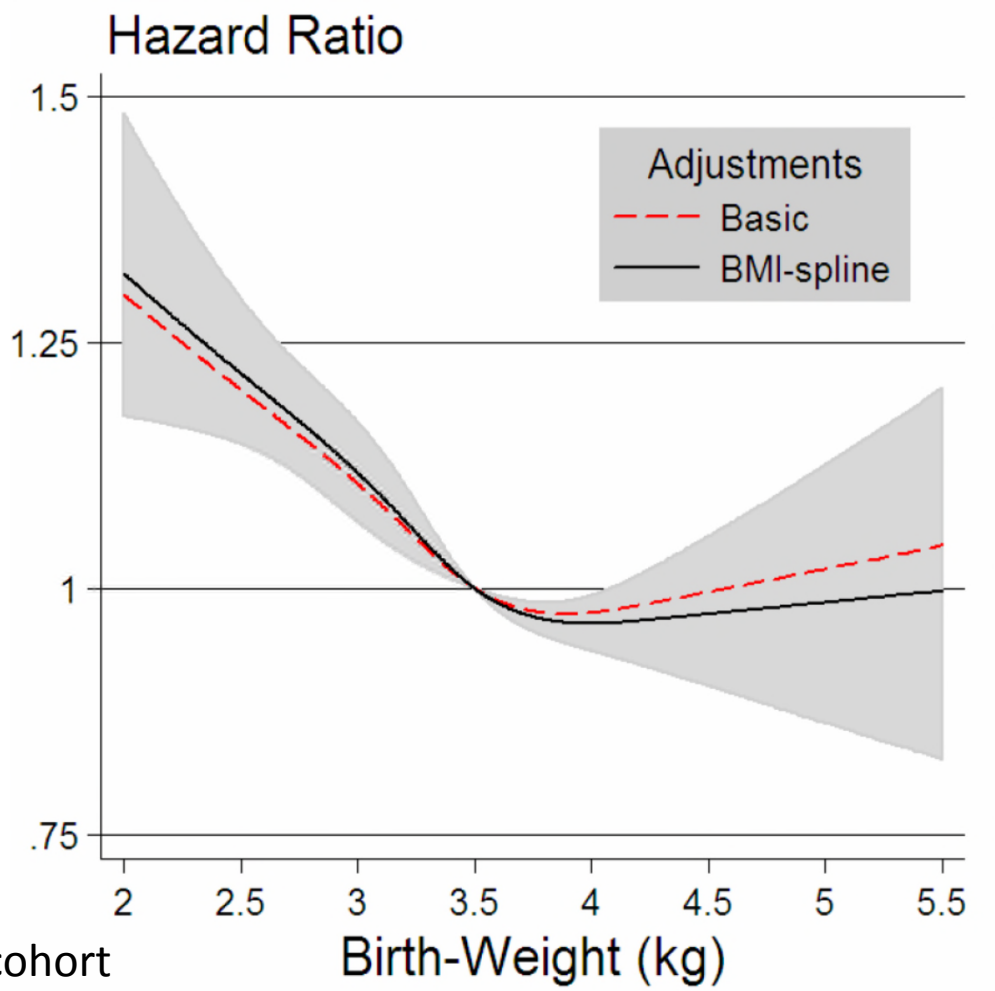
- More abdominal fat mass is harmful
- More peripheral fat mass is beneficial
- More lean body mass (to some level) is beneficial

It is likely that the net effect on mortality of these body compartments depends on their relative size and effect by size.


HR of mortality
1
3
5
7
60
80
100
120
140
WC (cm)

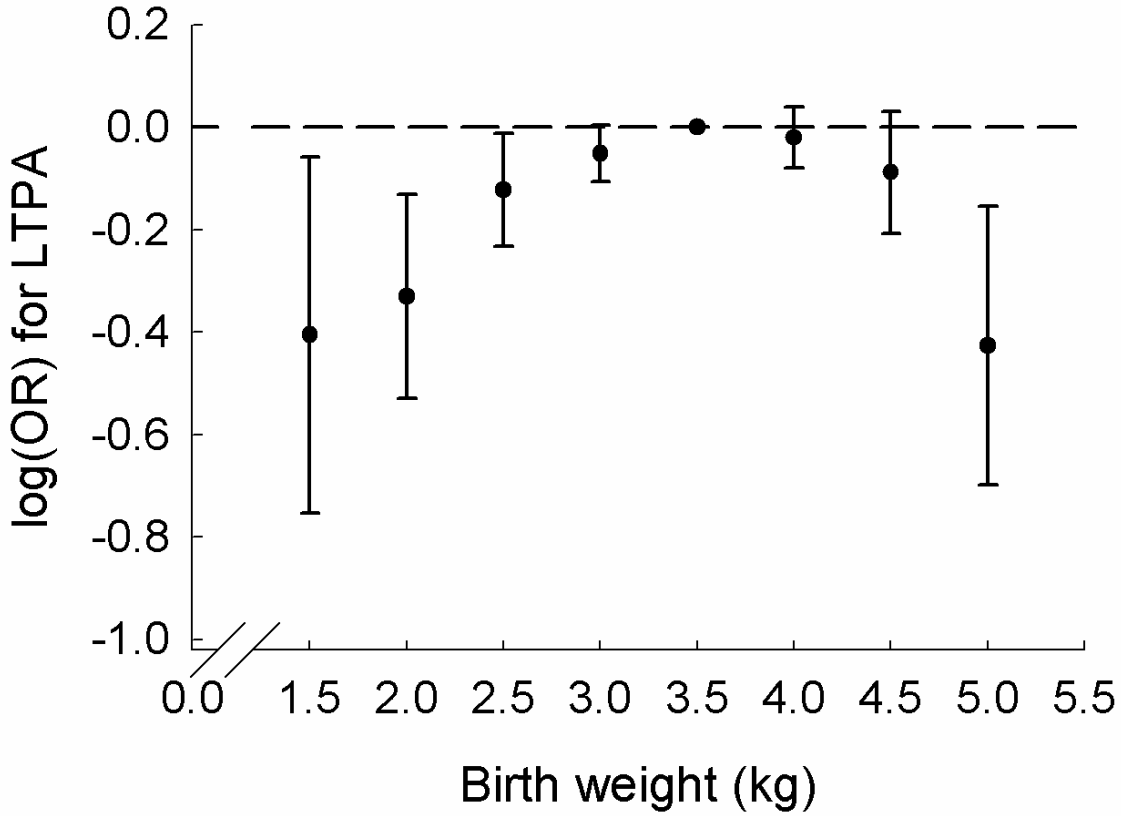

HR of mortality
.5
1
1.5
2
-10
0
10
20
dWC (cm)

Birth weight, childhood BMI and CHD in adulthood



Adjusted for sex and cohort

Birth weight and leisure time physical activity in adulthood



Meta-analysis pooling cohort and age and sex specific regression coefficients from logistic regression of birth weight as a categorical variable

Biochimica et Biophysica Acta 1801 (2010) 400–404

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Review

Obesity as a clinical and public health problem: Is there a need for a new definition based on lipotoxicity effects?

Thorkild I.A. Sørensen [a,*], Sam Virtue [b], Antonio Vidal-Puig [b]

[a] Institute of Preventive Medicine, Copenhagen University Hospitals, Copenhagen, Denmark
[b] Institute of Metabolic Science, Metabolic Research Laboratories, University of Cambridge, Box 289, Level 4, Addenbrooke's Hospital, Cambridge CB2 0QQ, United Kingdom

Assumption of inert TAG

- Accumulated evidence in both humans and animals suggest that the stored TAG in intracellular droplets is biologically inert and as such harmless
- This applies to TAG stored in adipocytes or elsewhere, including hepatocytes
- Seems to go as long as the cellular TAG deposits are expandable

Why not the TAG accumulation as such?

- A sizeable fraction of massively obese patients exhibits no fatty liver and no sign of the metabolic syndrome
- Patients with no, very little or dysfunctional adipose tissue (lipodystrophy) may have massive fatty liver and exhibit very severe signs of metabolic syndrome
- People with the genetic variant, PNPLA3 (Adiponutrin), is associated with fatty liver without or even with less signs of metabolic syndrome than in those without the variant

Link between obesity and ectopic fat deposition

- As long as the adipose tissue can expand by adipogenesis and cellular hypertrophy and thereby serve as a sink for excess fatty acids, TAG will not be stored elsewhere, neither in the liver
- When the adipose tissue for some reason approaches its limits of expandability and the excess exposure to fatty acids continues (due to fat intake and limitations in oxidation of fat), then ectopic TAG storage, including in the liver, begins
- This may lead to the metabolic syndrome and to necro-inflammation typical of NASH and what follows thereafter (fibrosis, cirrhosis)

Implications for epidemiology

- If the assumption of the inert TAG is true, then it has profound implications for an epidemiological approach to the study of the causes of obesity, NAFDL and its consequences, both metabolic and locally
- The assumption essentially makes the size of the TAG deposits in adipose tissue and elsewhere, inclusing the liver, irrelevant as such
- The size of these deposits is then just a positive marker of the likelihood that the expandability may be exhausted

Need for a redefinition or reclassification of obesity?

- The current definition and classification of obesity is based on the risk of adverse health effects associated with amount of TAG in the body.
- If the interpretations of the observations leading to the assumption of the inert TAGs accumulated in the liver and the abdomen is true then obesity needs to be characterised on the basis of what else is causing the harmful effects

Role of TAG accumulation may be confounded

- In epidemiology seeking to identify true causes of diseases – what makes some and not others sick in the populations - a confounder is a factor or feature that 1) has an effect on the risk of disease 2) is associated with the putative cause and 3) not a mediator of the effects of the putative cause
- If the TAG accumulation is an epiphenomenon that may or may not indicate the true processes leading to the harmful metabolic effects, the epidemiological study of the putative causal role of TAG accumulation is severely confounded

Implications for epidemiology

- This assumption of the inert TAG may have major implications for the epidemiological approach to the study of the causes of obesity and its consequences
- The assumption essentially makes the size of the TAG deposits (volume and weight) in adipose tissue and elsewhere, including the liver, irrelevant as such
- We need new measures of the risks asscociated with obesity, and with the fat accumulation in the liver and the abdomen
- To be useful, these measures should be able to predict the risk before any obvious adverse metabolic effects have emerged

Disconnections in the global epidemic of obesity and co-morbidities

- The obesity epidemic is followed by an epidemic of diabetes and cardiovascular diseases all over the world
- However, there is a disconnetion between the obesity epidemic and the occurrence of diabetes and cardiovascular diseases; some population, especially those of Asian ancestry, have much higher risk despite being much less afflicted by the obesity epidemic
- The degree of fat accumulation in the liver and the abdomen may be a better indicator of the risk in these populations, but perhaps not its cause

Implications for global public health actions

- If the assumption of the inert TAG is true - and it therefore is not the degree of fat accumulation in the liver and the abdomen as such that drives the disease process, but something else associated with it - then this has profound implications for the provision of epidemiological evidence that should guide the global public health actions toward the epidemic of diabetes and cardiovascular diseases, not least in the Asian populations.
- The achievements of HEPADIP in trying to find out what else than the fat accumulation as such is driving the disease process is its major contribution

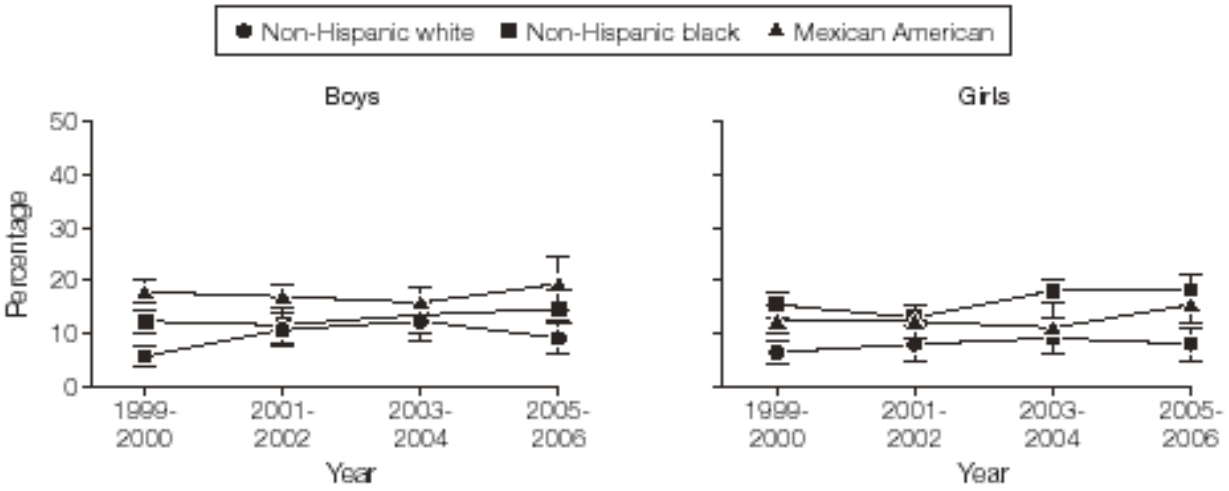
Conclusion

- Epidemiology need a better measure of what is going wrong in obesity than those based on amount of accumulated biologically inert TAG in adipose tissue and any other organ
- The current status of epidemiological evidence is not sufficient to understand the global public health problem of the epidemic of obesity and its co-morbidities
- Therefore, there is neither adequate evidence for the public health actions to be taken against the epidemic
- The HEPADIP-like work is needed to find the better measure of the risk of the co-morbidities!

U.S.A. children and adolescents

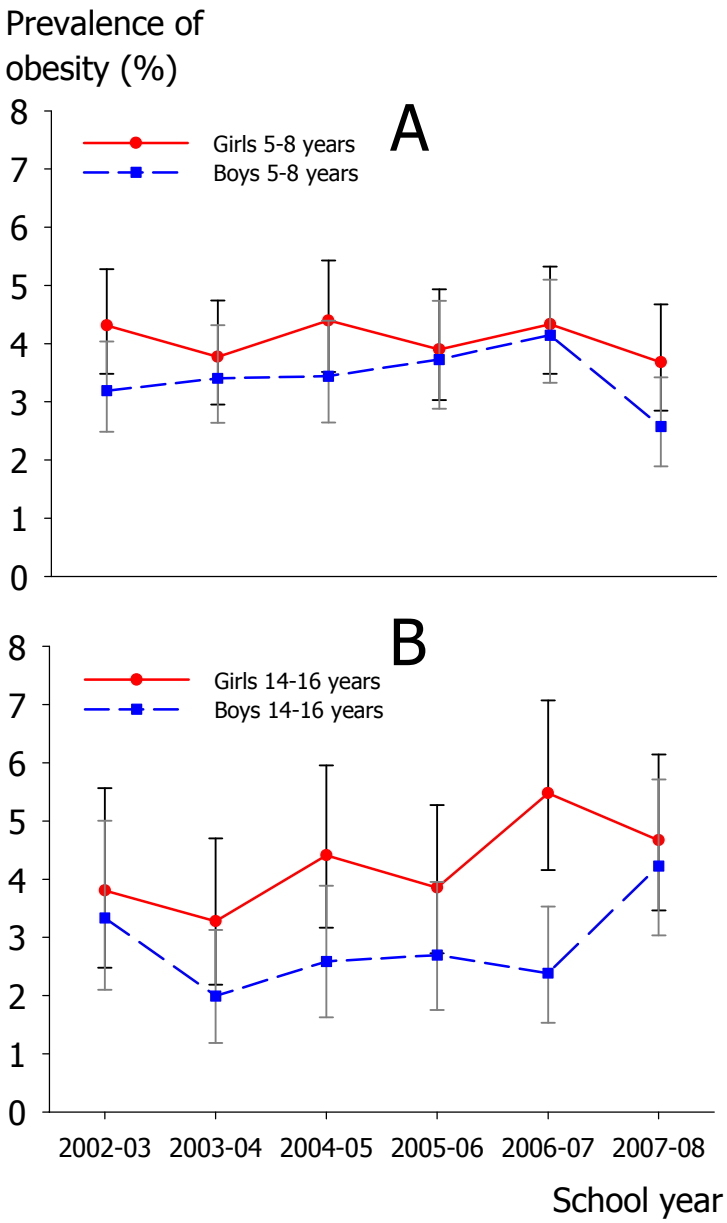
(National survey – 97th percentile)

Figure 1. Body Mass Index for Age at or Above the 97th Percentile by Race/Ethnicity in 1999-2006

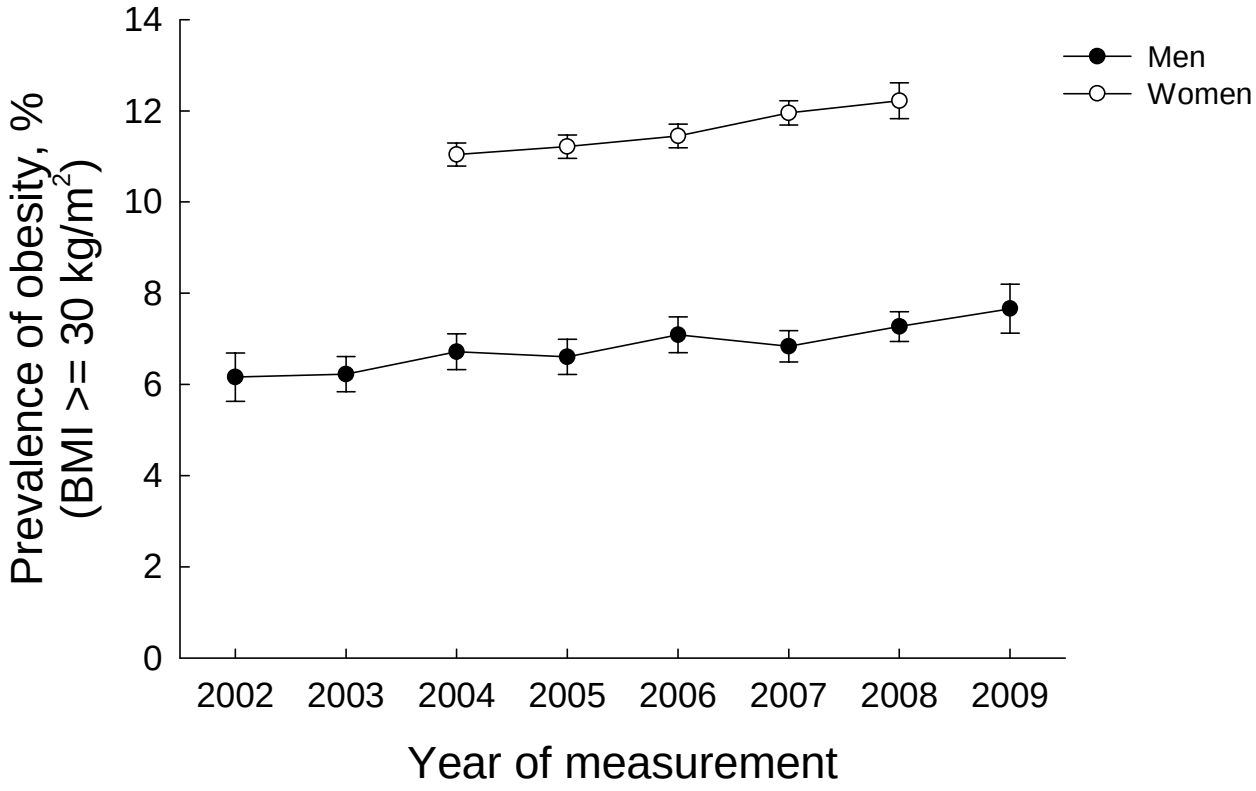


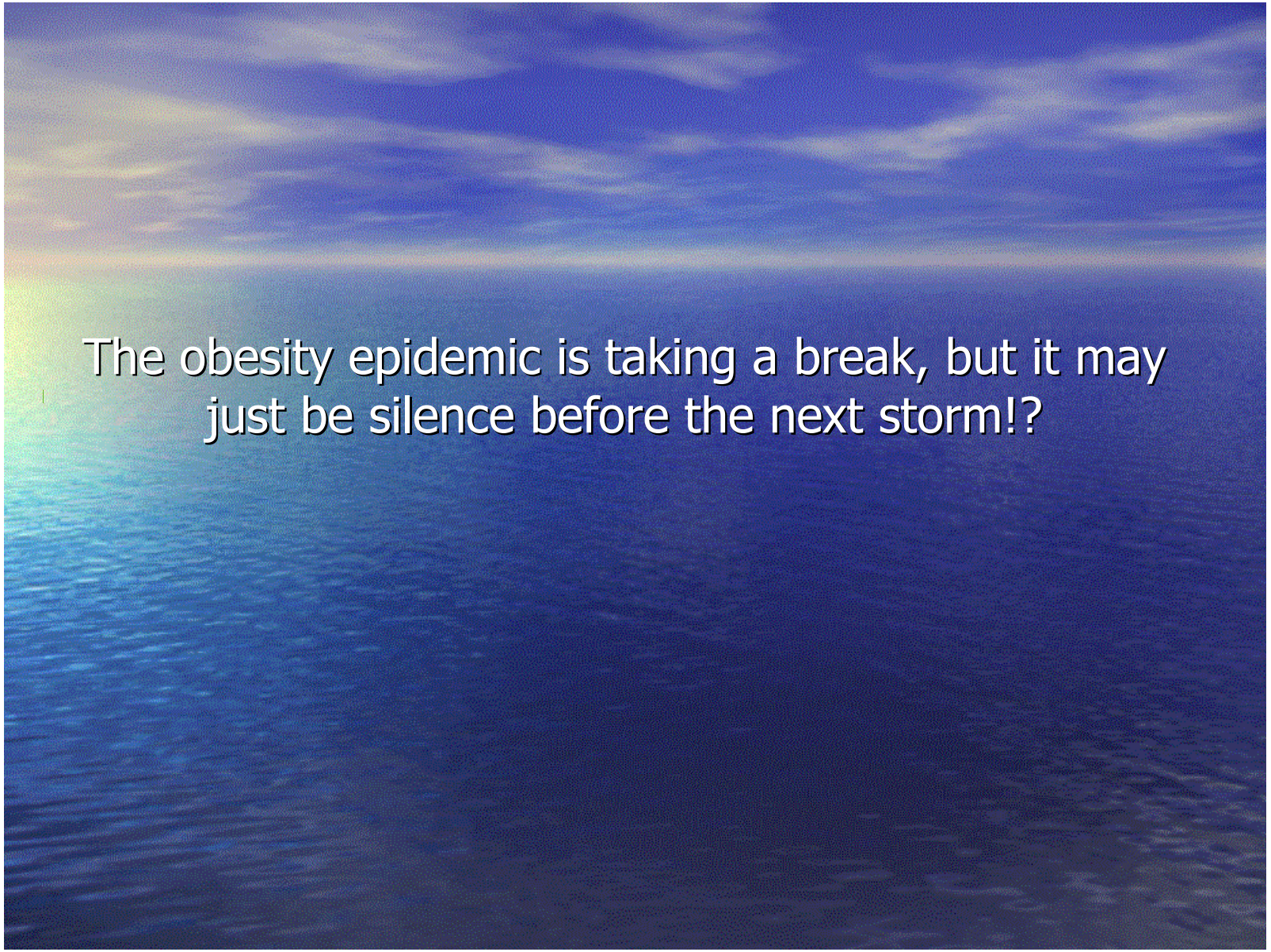
Error bars indicate 95% confidence intervals. Participants were aged 2 through 19 years.

Ogden et al. High body mass index for age among US children and adolescents, 2003-2006; JAMA, 2008.


Prevalence of obesity (%)
A
Girls 5-8 years
Boys 5-8 years
B
Girls 14-16 years
Boys 14-16 years
0
1
2
3
4
5
6
7
8
2002-03
2003-04
2004-05
2005-06
2006-07
2007-08
School year

Most recent trends in prevalence




The obesity epidemic is taking a break, but it may just be silence before the next storm!?