

NIMBioS Workshop
Modelling body weight regulation
Knoxville, Tennessee, USA
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Adding expandability limits of the various fat compartments and its metabolic consequences to models predicting body weight gain

Thorkild I.A. Sørensen, MD,
Dr Med Sci, Professor, Director
Institute of Preventive Medicine
Copenhagen University Hospital
Copenhagen, Denmark

www.ipm.regionh.dk; tias@ipm.regionh.dk
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Three steps toward a new model

- Summary of models of altered energy balance and body weight changes developed together with the mathematician, Edmund Christiansen.
- Introduction to the theory of adiposity as accumulation of biologically inert triacylglycerides (TAG), which leads to metabolic complications only when limits of TAG accumulation have been exceeded (lipotoxicity).
- Non-mathematical suggestions for adding the parameters of dynamics and limits of the size of TAG stores in various body compartments to the models.

The enigmas of obesity

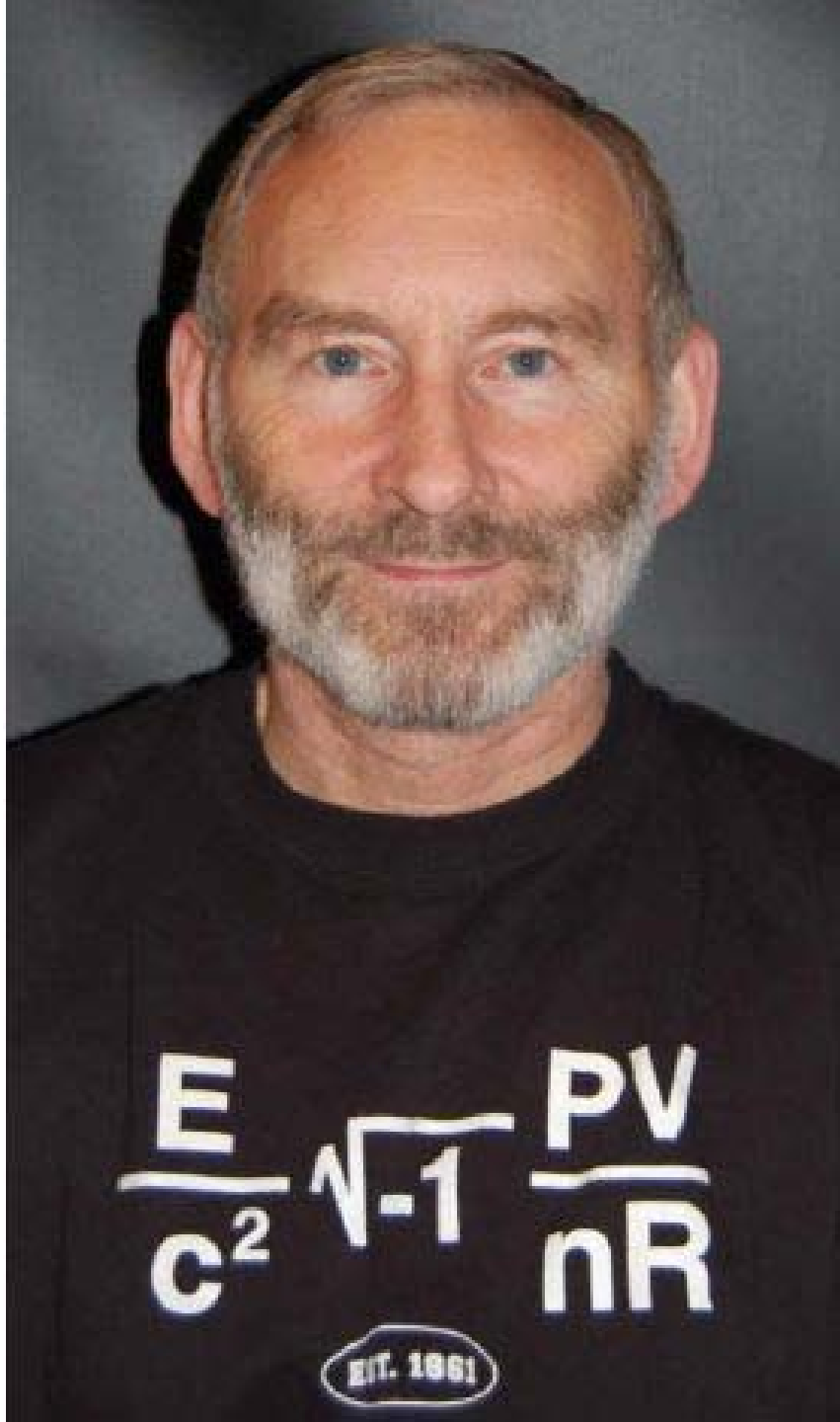
- The causes and the consequences of obesity
- Obesity reflects a preceding positive energy balance, implying an excess intake of energy relative to the needs, but what has caused it? Increased food intake, reduced physical activity, or even a primary tendency to accumulate fat?
- The more obese, the higher the risk of co-morbidities, but what is eliciting the risk while keeping many non-affected for long time, even among the most obese?

Why mathematical modeling?

- Improved predictions of physiological requirements for body mass change and obesity development, and hence for possible prevention
- More detailed understanding of the quantitative interplay between determinants of body mass and development of obesity
- Although such models do not allow inferences about causal sequences, they sets quantitative limits for the causal models
- Estimation of the requirements for measurements of the involved determinants, currently beyond the ability of available methods

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Edmund Christiansen

Born 1947, died 2007.

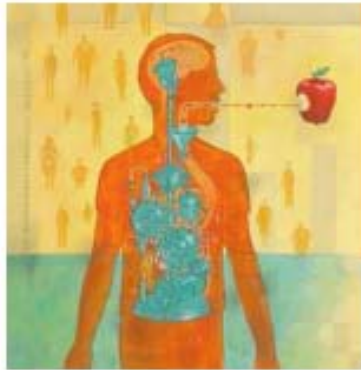
PhD in 1976 at MIT, Boston, USA.

Associate professor at Institute of mathematics and informatics, University of Southern Denmark.

Dr Science degree in 1993.

Research in numerical analysis

Highly appreciated teacher and colleague.



Mathematical Modeling of Human Metabolism and Body Weight Regulation

September 27 - 28, 2008 • Hyatt Regency Bethesda, Bethesda, MD



NIDDK NATIONAL INSTITUTE OF
DIABETES AND DIGESTIVE AND
KIDNEY DISEASES



Sunday, September 28, 2008

Quantitative Analysis of the Energy Requirements for Development of Obesity

Quantitative analysis of the energy requirements for development of obesity

Edmund Christiansen^{a,*}, Lars Garby^b, Thorkild I.A. Sørensen^c

^a*Department of Mathematics and Computer Science, University of Southern Denmark, Campusvej 55, Odense DK-5230, Denmark*

^b*Institute of Medical Biology, University of Southern Denmark, Odense, Denmark*

^c*Danish Epidemiology Centre, Institute of Preventive Medicine, Copenhagen University Hospital, Denmark*

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Feedback models allowing estimation of thresholds for self-promoting body weight gain

Edmund Christiansen^{a,†}, Andrew Swann^a, Thorkild I.A. Sørensen^{b,*}

^a*Department of Mathematics and Computer Science, University of Southern Denmark, Odense, Denmark*

^b*Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark*

Problem outlining, 1

- Weight gain eventually leading to obesity is usually a very slow process, around say 1 kg/year
- 1st law of thermodynamics applies as a basis of the energy balance equation
- The accumulated energy corresponds to about 1% of the energy intake
- Weight gain changes the components of the energy balance equation wherefore a 1% increase in energy intake not necessarily result in a gain of 1 kg/year

Problem outlining, 2

- Weight gain leads to an increased metabolic rate due to the metabolism in the added tissue
- The storage of energy as novel tissue requires energy by itself that cannot be recovered by conversion of the stored tissue to heat (2nd law of thermodynamics)
- Since the absolute values of energy intake and output (by physical activity) may change during weight gain, they must be taken into account, not just the difference

- If a person in steady state, i.e. energy intake equals energy expenditure, instantaneously changes energy intake and/or physical activity level and keep the new values constant, what is the resulting change in steady-state body weight?
- In the same situation, what is the rate of weight change?
- Assuming a constant rate of increase in body weight, for example 1 kg/year, by how much does the energy intake exceed the energy intake in steady state?
- Can the theory predict the result of difficult observations in humans that require long observation periods?

Nomenclature

<i>BMR</i>	basal metabolic rate (MJ/d)	<i>BM</i>	body mass (kg)
<i>TEE</i>	total energy expenditure (MJ/d), not including <i>EE_c</i> below	<i>BM_{ss}</i>	steady-state body mass for constant <i>EI</i> and <i>PAF</i> .
<i>PAF</i>	physical activity factor, defined as <i>TEE/BMR</i>	<i>FM</i>	fat mass (kg)
<i>EI</i>	energy intake (MJ/d)	<i>LM</i>	lean mass (kg)
<i>EI_{ss}</i>	steady-state energy intake for given body mass and <i>PAF</i>	<i>f_r</i>	fraction of fat in new tissue (= $\Delta FM / \Delta BM$)
<i>EE_c</i>	energy expenditure used to convert excess energy into tissue	<i>e_f, e_l</i>	energy stored per kilo fat, resp. lean, tissue (MJ/kg)
<i>C</i>	total content of combustible energy in the body (MJ)	<i>k_f, k_l</i>	basal metabolic rate per kilo fat, resp. lean, tissue (MJ/(kg d))
		<i>e, e_f, e_l</i>	efficiency in the conversion of energy to new tissue (see below)

1. The body mass can be divided into fat and lean tissue, each of which has a specific energy content, c_f and c_l , and a specific basal metabolic rate, k_f and k_l .
2. The conversion of surplus energy in intake to fat, resp. lean, tissue requires specific amounts of energy, given by the efficiencies e_f and e_l .
3. Energy expenditure only depends on the fat mass FM , the lean mass LM , and the physical activity factor PAF .
4. Efficiency in energy intake is not regulated by the energy imbalance.
5. Efficiency in energy intake does not depend on the composition of food, especially with regard to the macro-nutrient content.
6. The fraction of fat in added tissue f_r is independent of body mass.

Basic theory

Conservation of combustible energy leads to the following differential equation for positive energy balance:

$$\frac{dC}{dt} = EI - PAF BMR - EE_c. \quad (1)$$

The steady-state equation is

$$EI = BMR PAF. \quad (2)$$

In Eqs. (1) and (2) EI and PAF are under direct control by the individual, while BMR depends on body mass and body composition.

General model for body mass changes

$$\begin{aligned} \frac{dBM}{dt} &= \frac{EI - PAF(BMR_0 + (k_f f_r + k_l(1 - f_r))(BM - BM_0))}{c_f f_r / e_f + c_l(1 - f_r) / e_l}. \end{aligned} \quad (15)$$

The efficiency in conversion of surplus energy into new tissue has no influence on steady state, but has a direct proportional influence on the rate of weight increase during periods of positive energy imbalance.

Model testability

A main point of the theory is that the quantities referred to can be, and have been, measured. If, for example, new data should reveal the quantitative dependence of the fat fraction on body mass, then this can easily be included in the model. Our simplifications are not made in order to simplify the model, but sufficient data are needed to justify a more refined model.

The present model is intended to be an approximation under normal conditions (no starvation or over-feeding and no extreme food composition) for “normal” adults

Quantitative analysis of the energy requirements for development of obesity

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Problem outlining, 3

- According to the model developed, weight gain with maintained PAF leads to increased food intake corresponding to the needs to satisfy the increased metabolism and the deposition of energy as body mass
- Beyond this, weight gain by itself may induce - through a variety of hypothetical mechanisms – changes in food intake and physical activity
- A number of studies have suggested that physical activity decline following increasing body weight

Problem outlining, 4

- In theory, combinations of increase in food intake and decline in physical activity as a consequence of weight gain may create settings leading to further weight gain
- The model for weight gain can be extended to allow for this feedback that make the regulation unstable and weight gain self-promoting
- This extended model can be used to estimate the limits of stability beyond which self-promoting weight gain may take place

Modeling stability vs instability

- Edmund Christiansen: classical, well established mathematical models for dynamic systems.
- Examples:
- Microphone-loudspeaker interaction
- Bridges exposed to various external forces

Notation

BM	body mass, kg
FM	fat mass, kg
FFM	fat free mass ($= BM - FM$)
C	total energy stored in the body, MJ
EI	energy intake, MJ/d
BMR	basal metabolic rate, MJ/d
$DIEE$	diet-induced energy expenditure ($= 0.1EI$)
CE	conversion energy used to convert energy in intake to new tissue, MJ/d
PAF	physical activity factor ($= TEE/BMR$)
TEE	total energy expenditure ($= DIEE + CE + PAF \cdot BMR$)
f_r	fraction of fat in new tissue ($\Delta FM/\Delta BM$), assumed to be independent of BM
c_f, c_{ff}	energy stored per kilo fat, respectively, fat-free, tissue, MJ/kg
k_f, k_{ff}	basal energy expenditure per kilo fat, respectively, fat-free, tissue, MJ/(kg d)
e_f, e_{ff}	efficiency in the conversion of energy to fat, respectively,
c	increase in stored energy per kilo added tissue derived in Eq. (4)
k	increase in energy expenditure per kilo added tissue derived in Eq. (6)
FB_{EI}	feedback parameter from BM to EI
FB_{PAF}	feedback parameter from BM to PAF
PAF_{max}, PAF_{min}	maximum and minimum allowable values for PAF
$PAFR$	relative physical activity factor ($= (PAF - PAF_{min}) / (PAF_{max} - PAF)$)
BFB_{PAF}	parameter controlling feedback from BM to PAF in logistic model (12).

Incorporation of feedback, 1

The incorporation of the feedback may be carried out in many different ways with different assumptions, but for convenience, the simplest model is preferable and developed in the following. We assume that the feedback is proportional to $BM - BM_0$ while acknowledging that this may hold only for small weight gains:

$$\begin{aligned}EI &= EI_0 + FB_{EI}(BM - BM_0), \\ PAF &= PAF_0 - FB_{PAF}(BM - BM_0).\end{aligned}\tag{9}$$

FB_{EI} and FB_{PAF} are constant feedback parameters defined by

$$\begin{aligned}FB_{EI} &= \frac{EI - EI_0}{BM - BM_0} = \frac{\Delta EI}{\Delta BM}, \\ FB_{PAF} &= -\frac{PAF - PAF_0}{BM - BM_0} = -\frac{\Delta PAF}{\Delta BM}.\end{aligned}$$

Incorporation of feedback, 2

$$\frac{dBM}{dt} = \frac{1}{c}(BM - BM_0) \left(\begin{array}{l} 0.9FB_{EI} + FB_{PAF} \cdot BMR_0 - k \cdot PAF_0 \\ + k \cdot FB_{PAF} (BM - BM_0) \end{array} \right). \quad (10)$$

If the second parenthesis in Eq. (10) is negative, then dBM/dt will have the opposite sign of $BM - BM_0$ and hence $BM = BM_0$ is a stable solution. This is the case if FB_{EI} and FB_{PAF} are small. However, if $0.9FB_{EI} + FB_{PAF} \cdot BMR_0 - k \cdot PAF_0 > 0$, then the body weight is unstable at initial $BM = BM_0$: a small increase in body mass will imply a positive dBM/dt , and mass increase is self-promoting. Here we use that the last term in the parenthesis, the only non-constant term, is positive for $BM > BM_0$. We are thus lead to the following condition for instability and self-promoting weight change:

$$0.9FB_{EI} + FB_{PAF} \cdot BMR_0 > k \cdot PAF_0. \quad (11)$$

As stated, the linear feedback model (9) may well hold only for small weight gains. One potential problem is that unrealistic values of PAF can be produced for large deviations of BM from BM_0 . Mathematically there are many ways to address this problem. Indeed, as long as the linearization of the feedback agrees with (9), then one obtains the same instability criterion (11). One such modification that takes into account physiological bounds, PAF_{max} and PAF_{min} , for allowable values of PAF is given by a logistic model. Fitting this to the linearization (9), we obtain explicitly

$$PAF(t) = PAF_{min} + \frac{(PAF_{max} - PAF_{min}) \cdot PAFR_0}{PAFR_0 + \exp(BFB_{PAF} \cdot (BM(t) - BM_0))}, \quad (12)$$

where $PAFR_0 = (PAF_0 - PAF_{min}) / (PAF_{max} - PAF_0)$ is the initial relative PAF and $BFB_{PAF} = FB_{PAF} \cdot PAFR_0 / (PAF_{max} - PAF_{min})$ is the new parameter controlling the feedback. A similar feedback model may also be used for EI . As will be seen below, this logistic model agrees very closely with that produced by the linear feedback (9) for BM near BM_0 (within 10% in the examples). In such a range the linear model is clearly to be preferred because of its simplicity.

Comparison of models w/wo feedback

The difference between the former model described in Christiansen et al. (2005) and the one presented here can be exemplified in the requirements to gain a certain amount of body weight with a fixed $PAF = 1.5$, say about 10 kg in two years for a man with $BM(0) = 80$ kg, $BMR_0 = 7.8$ MJ/d. Under the former model, this will be achieved by adding 1 MJ/d to the energy intake, and about half of the gain will be achieved during the early part of the first of the 2 years. Under the proposed feedback model, with $FB_{PAF} = 0.005$ kg⁻¹, $FB_{EI} = 0.15$ MJ/d, the same weight gain will be achieved over 2 years by an initial 1% ≈ 0.1 MJ/d increase in energy intake with the major part of the weight gain taking place during the second year. Thus, allowing for the feedback may considerably reinforce the effects of even rather small primary excess intakes.

Eating out of control

The conditions under which this self-promoting process emerges are clearly dependent on the energy intake. The observation that “many obese and weight-gaining individuals claim that their eating is out of (their) control”, Blundell and Gillett (2001), suggests that the threshold for eliciting the self-promoting weight gain may be promoted by such a lack of control of energy intake. However, the model also shows that the

Jean Mayers threshold of PA

of energy intake. However, the model also shows that the likelihood of exceeding the limits for a stable system is greater if the physical activity is lower. This leads to a new interpretation of the observations by Mayer et al. (1954, 1956) and Schoeller (1998) that a threshold of physical activity should be exceeded in order to maintain energy balance. In today's sedentary population it is possible that many individuals have a minimal physical activity level, which cannot be reduced further. In such cases there cannot be a negative feedback to physical activity; however, PAF_0 on the right-hand side of condition (11) is so small that instability will occur for smaller values of FB_{EI} than otherwise.

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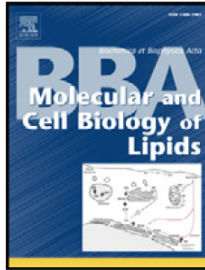


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Review

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



Usefulness of measures of accumulated TAG?

- Can we use measures of fat accumulation as TAG droplets in cells as tools to solve the public health problems of the obesity-diabetes epidemic, given that the TAG is biochemically and, hence, most likely also biologically inert?
- Why should the body's use of nature genius invention of storing biological material in the form of TAG as an energy reserve, mobilizable in times of shortness of energy supplies, be harmful?



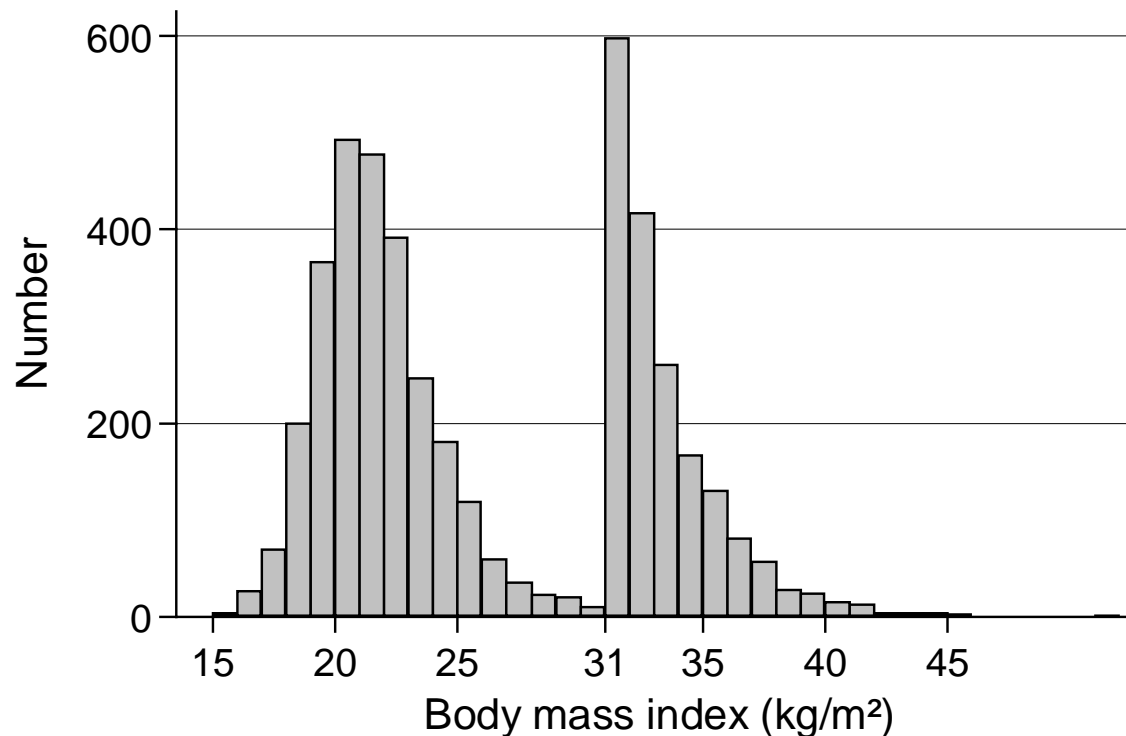
Health effects associated with fatness, i.e. amount of stored TAG, indicated by BMI

- The U- or J-shaped relation between mortality and BMI (the risk function) is indisputable, based on multiple studies of millions of people.
- The position of the nadir, usually between BMI 22 – 25, but the slopes of the ‘arms’ may differ between population segments.
- The left arm is often assumed to reflect underlying confounding by harmful behaviors (smoking), and the right arm is assumed to reflect effects of increasing fatness, leading to a variety of diseases with increased risk of dying.

Comparison of mortality and morbidity in obese young men with randomly selected young men throughout their adult lives

Study of 360,000 Danish young men examined at draft boards when around 19 years old during the years 1943-1977:

Selected all 1930 men with BMI ≥ 31 kg/m², and compared them with 3601 men sampled at random as 1% of all



ORIGINAL ARTICLE

Lifelong doubling of mortality in men entering adult life as obese

E Zimmermann^{1,2}, C Holst¹ and TIA Sørensen¹

¹*Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark and* ²*Institute of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark*

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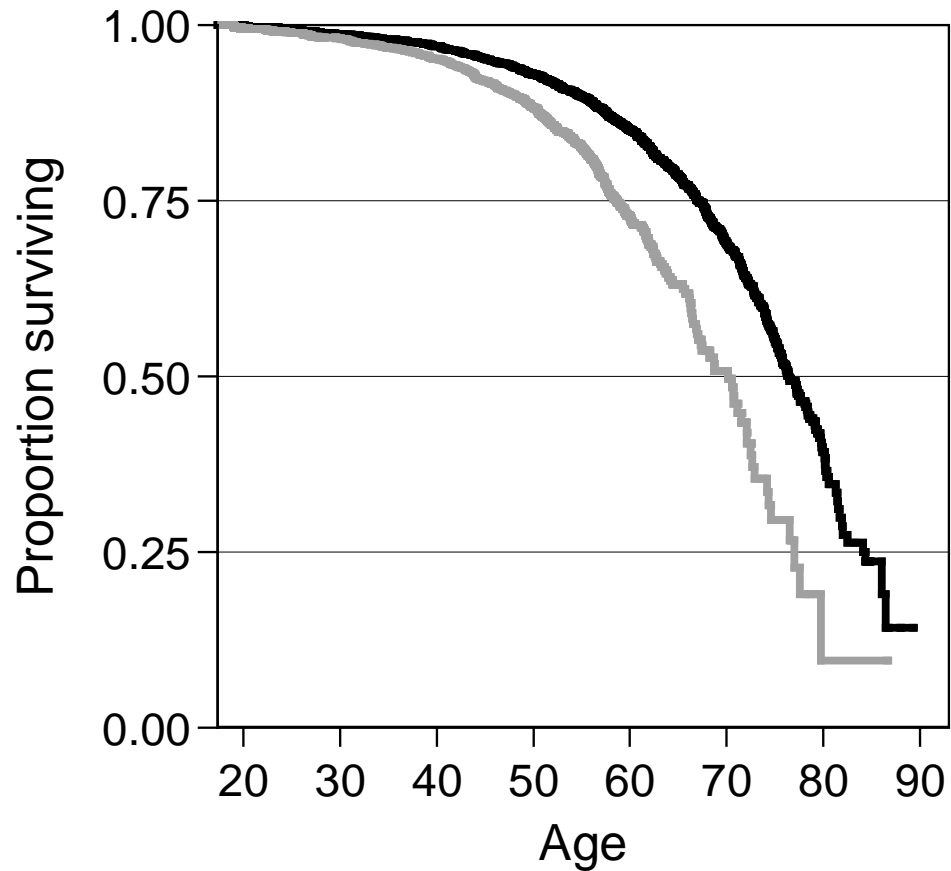


Morbidity, Including Fatal Morbidity, throughout Life in Men Entering Adult Life as Obese

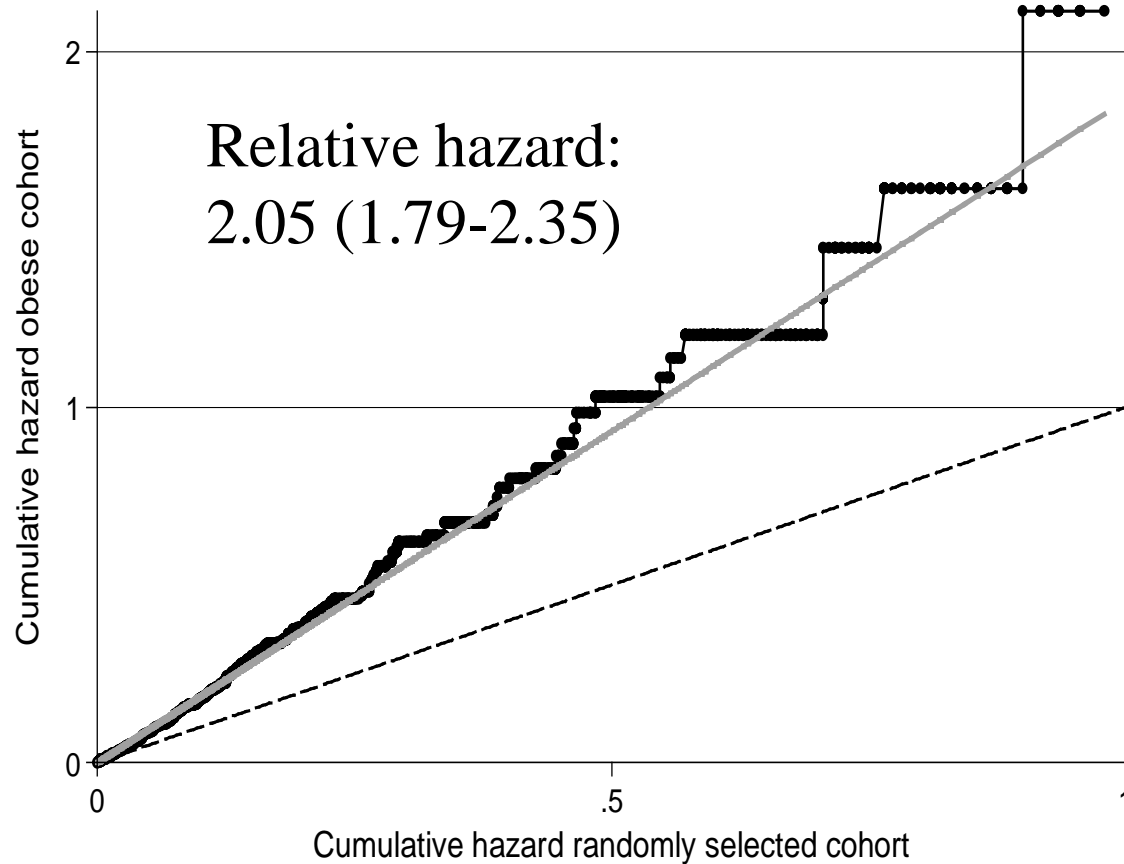
Esther Zimmermann^{1,2*}, Claus Holst¹, Thorkild I. A. Sørensen¹

1 Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark, **2** Institute of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

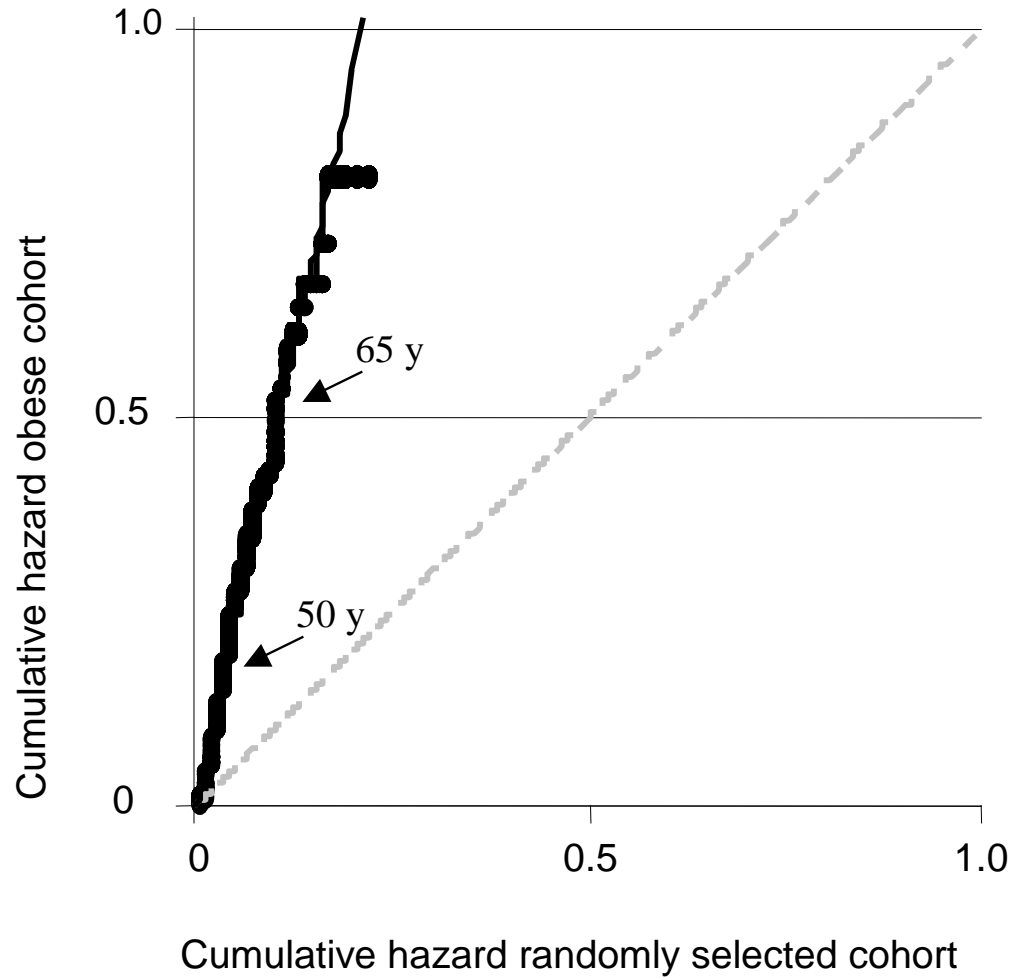
Kaplan Meier plots for the obese cohort (grey line)
and the randomly selected cohort (black line)



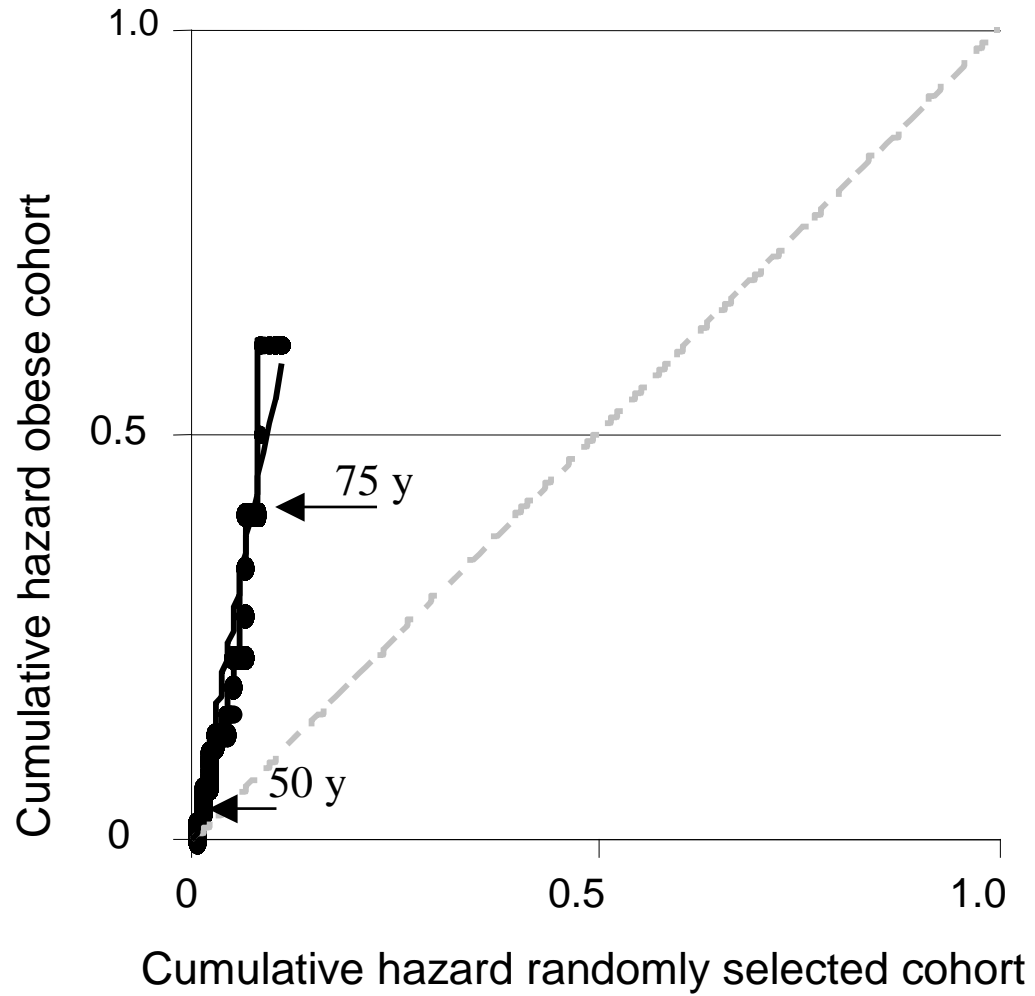
Double cumulative hazard plot at corresponding ages of total mortality of the obese cohort versus the randomly selected cohort



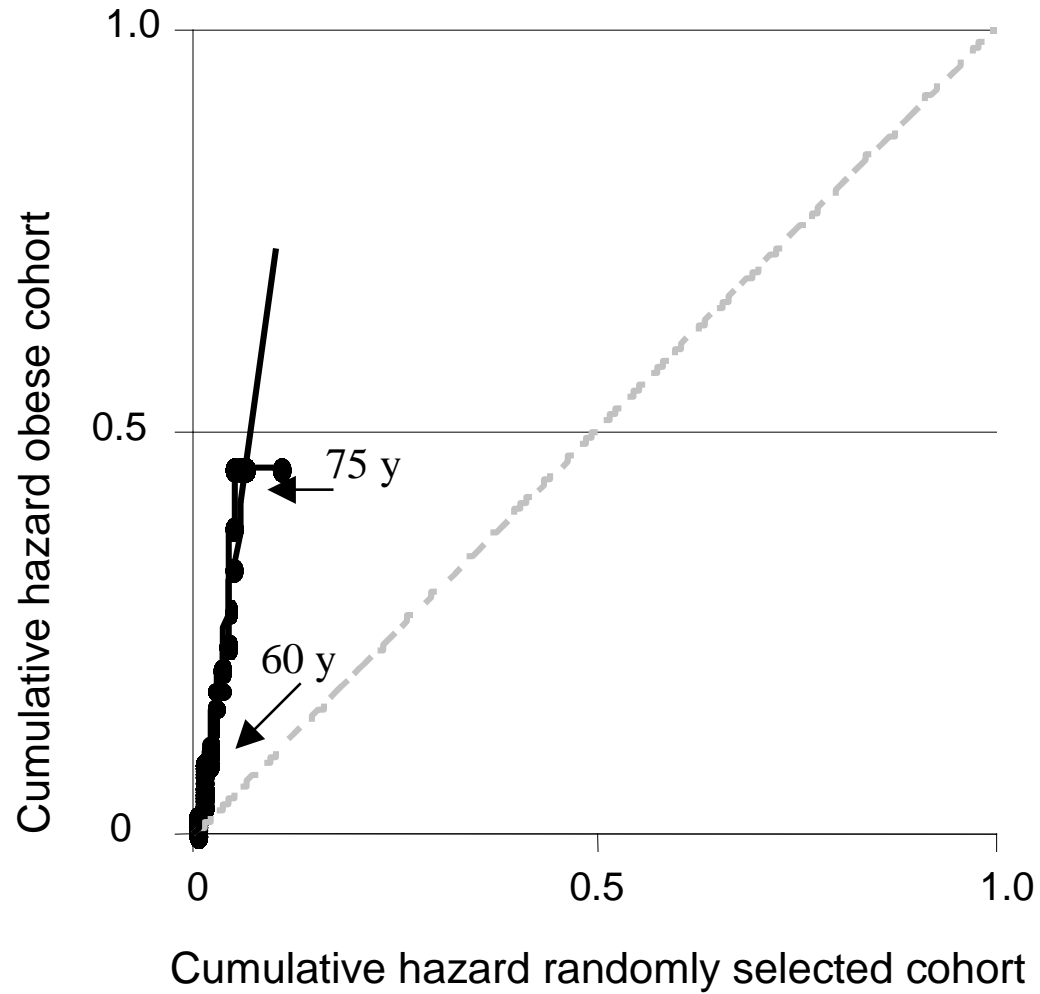
Incidence of diabetes: RR 4.92 (4.14-5.85)



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



Prevalent diabetes at death RR 6.83 (4.62-10.09)



Long-term influences of body-weight changes, independent of the attained weight, on risk of impaired glucose tolerance and Type 2 diabetes

Eva Black¹, C. Holst², A. Astrup¹, S. Toubro¹, S. Echwald³, O. Pedersen^{3,4} & T.I.A. Sørensen^{2,5}

Diabetic Medicine 2005; 22:1199–1205.

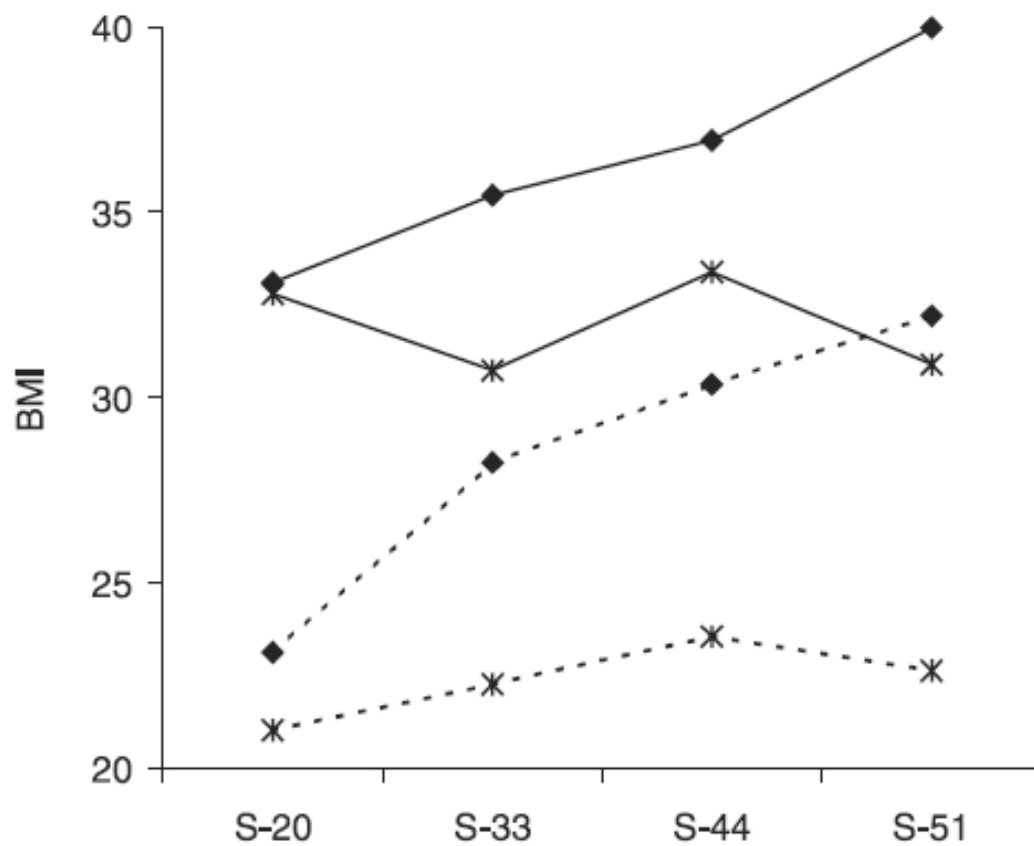


Figure 1 Body-weight history by selected levels of risk of impaired glucose tolerance in middle-aged, 'healthy' men. Mean BMI (kg/m^2) at the four surveys of obese (solid lines) and control (broken lines) subjects at equally high (◆) and low (✱) levels of risk of IGT at S-51. See Statistical analysis for details.

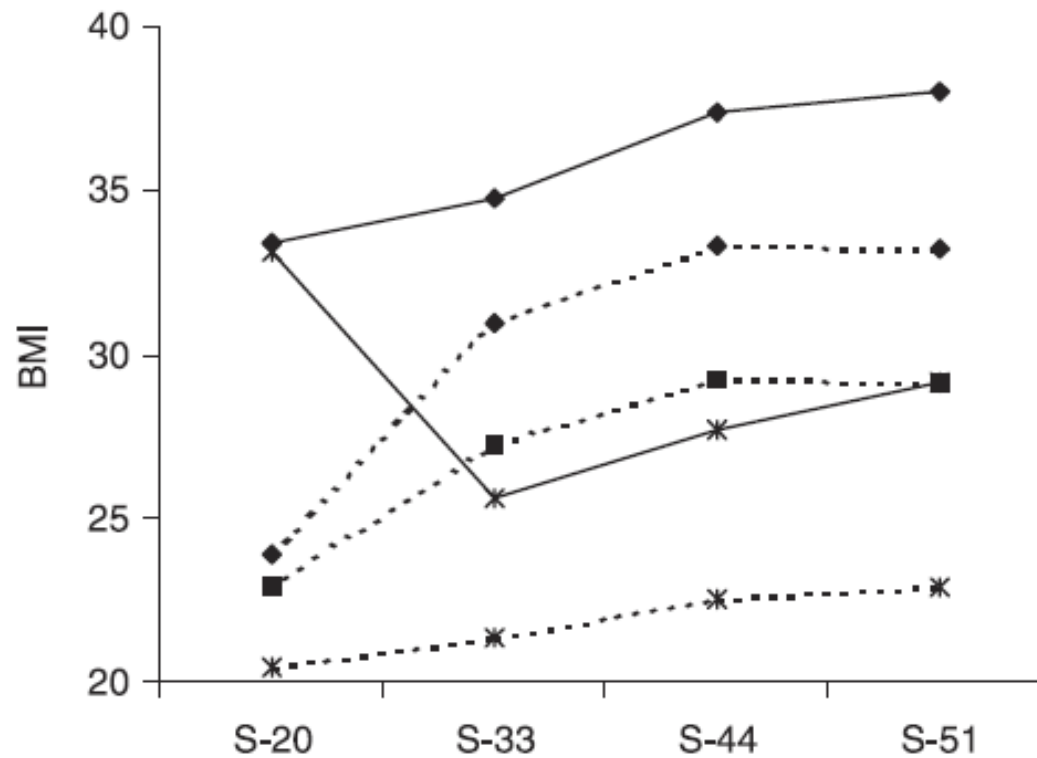


Figure 2 Body-weight history by selected levels of risk of Type 2 diabetes in middle-aged 'healthy' men. Mean BMI (kg/m^2) at the four surveys of obese (solid lines) and control (broken lines) subjects at equally high (◆) and low (✱) levels of risk for Type 2 diabetes at S-51. In addition, the figure shows the next to the high-risk level (■) in the control group. See Statistical analysis for details.

Weight change and diabetes

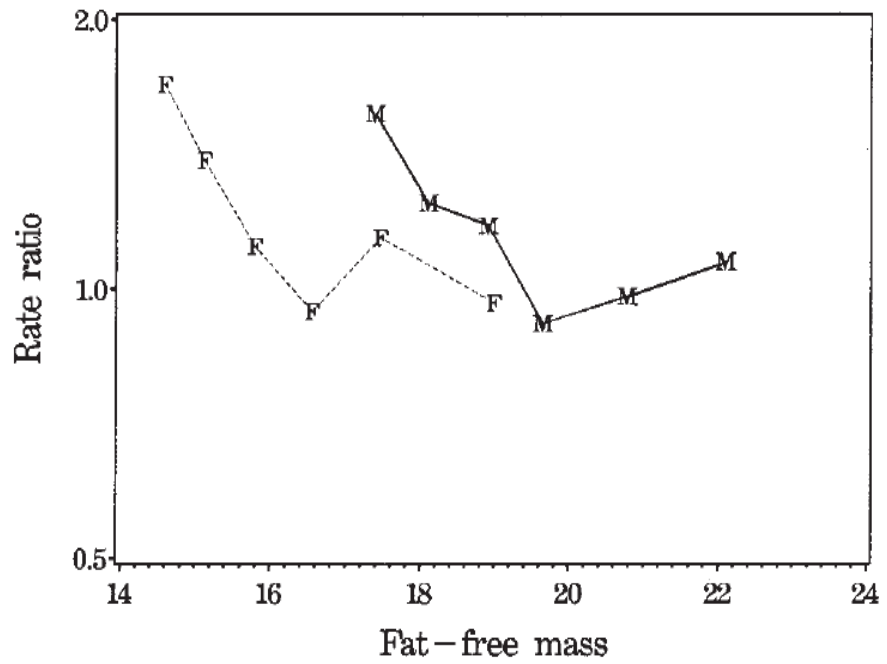
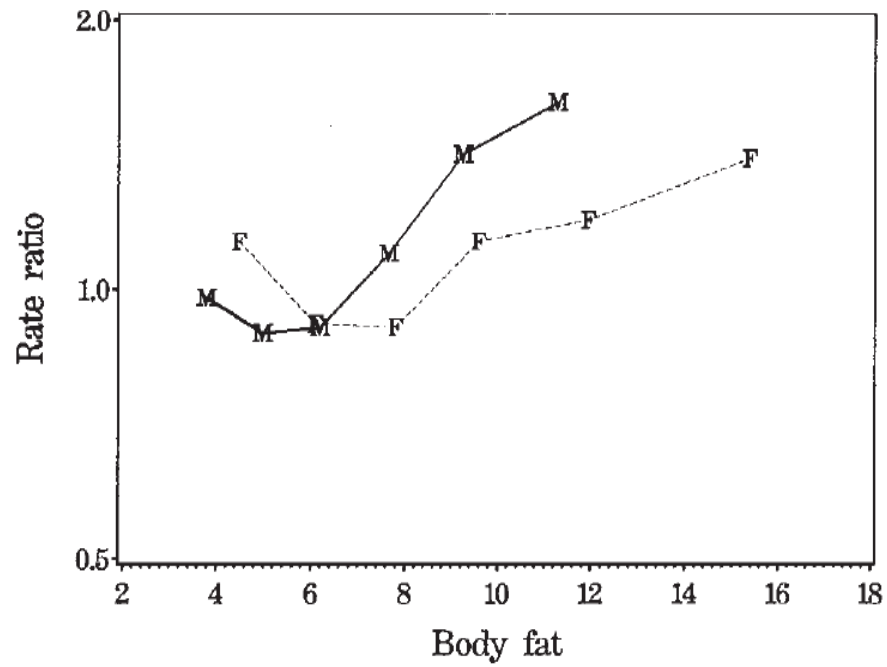
- For any given BMI, the risk of IGT was higher the greater the weight gain since age 20, and weight gain during both the early and later ages contributed to the increased risk.
- Obese men, maintaining weight since age 20, had lower risk of IGT than non-obese men who became similarly obese by age 51.
- The risk of Type 2 diabetes increased by weight gain in early adult life, but not by more recent weight gain in the later periods, probably because of the development of Type 2 diabetes leading to weight loss.

Health effects associated with body composition and body fat distribution

- Multiple studies strongly suggest that the body compartments may have different impact on health.
- More abdominal fat mass may be harmful.
- More peripheral fat mass may be beneficial.
- More lean body mass (to some level) may be beneficial.
- The net effect on the association of mortality with these body compartments may depend on their relative size and effect by size.
- The use of terms like ‘impact’ and ‘effect’ should not be interpreted as causation

Body Fat and Fat-Free Mass and All-Cause Mortality

Janne Bigaard, Kirsten Frederiksen,* Anne Tjønneland,* Birthe Lykke Thomsen,* Kim Overvad,† Berit Lillienthal Heitmann,‡ and Thorkild I.A. Sørensen‡*



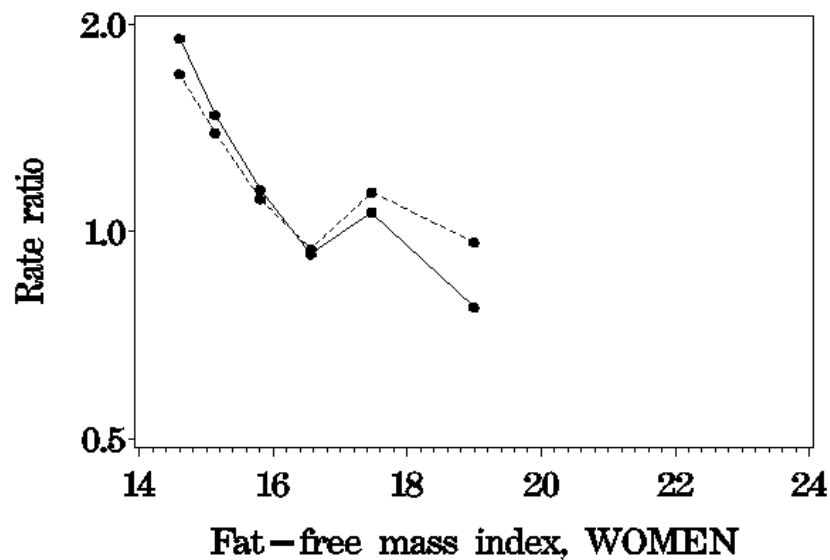
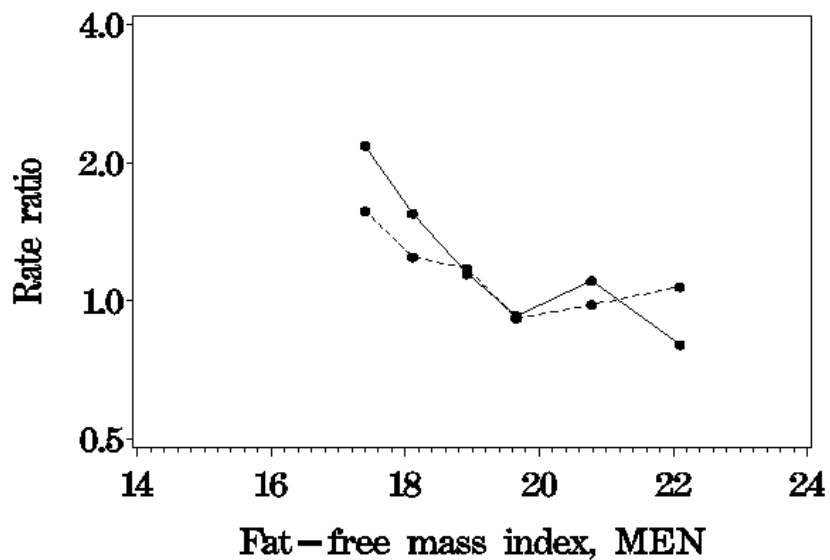
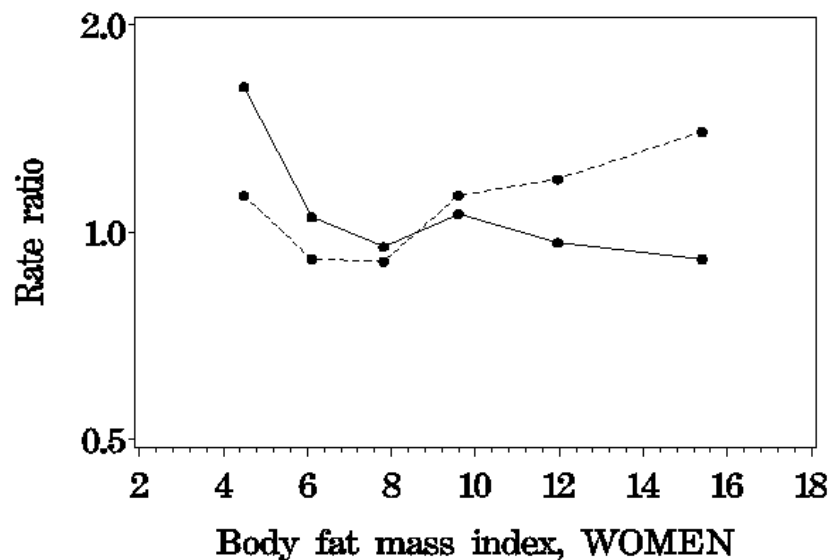
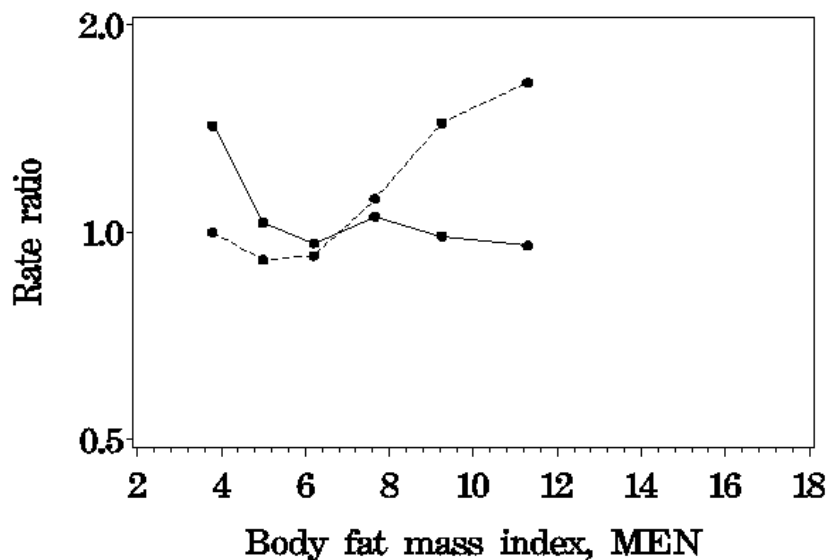


International Journal of Obesity (2005) 29, 778–784

Waist circumference and body composition in relation to all-cause mortality in middle-aged men and women

J Bigaard^{1*}, K Frederiksen¹, A Tjønneland¹, BL Thomsen¹, K Overvad^{2,3}, BL Heitmann⁴ and TIA Sørensen⁴

Body composition, adjusted for waist circumference, in relation to mortality in the DCH cohort



Key questions for epidemiologists

- Are the detrimental effects due to the TAG accumulation in the abdomen and perhaps in ectopic sites, especially the liver, which often is associated with abdominal obesity?
- There are several reasons to doubt if it is the TAG accumulation as such that is driving the disease processes.
- The TAG accumulation itself may not cause any harm, and may even be beneficial – as just being the optimal way of storing reserve energy?

Clinical evidence for inertness of TAG

- A sizeable fraction (10-20%) 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 a genetic variant in *PNPLA3* (encoding Adiponutrin), is associated with fatty liver without or even with less signs of metabolic syndrome than in those without the variant

Experimental evidence for inertness of TAG

- Accumulated experimental evidence in animals suggest that the stored TAG in intracellular droplets is biologically inert and as such harmless.
- This applies to TAG stored in adipocytes and elsewhere, including hepatocytes.
- Seems to go as long as the cellular TAG deposits are expandable.
- Blocking the addition of the 3rd fatty acids in TAG induces severe metabolic disturbances (DAG, ceramides)

Expandability theory defining upper limits of TAG storage

- Expandability of the subcutaneous adipose tissue is limited by number and size of adipocytes.
- When the expandability limits are approached, extra fat accumulation begins in the visceral depots, also limited by number and size of adipocytes.
- When the visceral depot limits are approached, fat accumulation begins in the liver and other ectopic sites.
- Exceeding limits of TAG storage in available depots may induce a state of lipotoxicity.



Lipotoxicity effects as consequence of exhausted TAG storage

- When either storage of free fatty acids (FFA) in TAG is exhausted, and beta-oxidation of FFA as energy source cannot use available FFA, a cascade of cellular toxic effects may follow, both in adipose tissue and elsewhere
- ROS activation, mitochondrial dysfunction, and inflammatory processes may be induced and the cellular insulin signalling may be disturbed
- Insulin resistance may develop, and following this the metabolic syndrome, and eventual diabetes and other sequela

The theory may explain 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 disconnection between the obesity epidemic and the occurrence of diabetes and cardiovascular diseases.
- Some populations, especially those of Asian ancestry, have much higher risk despite being much less afflicted by the obesity epidemic.

May be the obesity epidemic is good!?

- The occurrence of the obesity epidemic, not least in the Western world, may be seen as beneficial in the counterfactual sense that had we not had the obesity epidemic, then the diabetes epidemic would have been much worse, as it is now in Asia.
- At the population level, the obesity epidemic may be seen as the attempts to protect the population against the risk of diabetes and other obesity-associated conditions!
- The reason for the higher incidence of diabetes in the Asian population may be the limited capacity to store TAG.

There is a 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 TAG irrespective of where it is accumulated is true, then obesity needs to be characterised on the basis of what else is causing the harmful effects.
- A measure indicating current residual capacity to either store FFA as TAG or oxidise them may be the tool.

Derived specific research questions

- How much TAG can be stored and how do we measure it before the limits are reached?
- What is the nature and determinants of the storage capacity?
- What is the role of a positive energy balance reflected in the microaccumulation of TAG that leads to obesity?
- How can the TAG storage capacity be overloaded?
- Why is overloading causing metabolic dysfunction and health problems?
- Can we really interpret the obesity epidemic as good?
- What can be done to prevent and treat FFA overloading?

Obesity Defined as Excess Storage of Inert Triglycerides – Do We Need a Paradigm Shift?

Thorkild I.A. Sørensen

Institute of Preventive Medicine, Copenhagen University Hospitals, Capital Region of Denmark, Denmark

Three steps toward a new model

- Summary of models of altered energy balance and body weight changes developed together with the mathematician, Edmund Christiansen.
- Introduction to the theory of adiposity as accumulation of biologically inert triacylglycerides (TAG), which leads to metabolic complications only when limits of TAG accumulation has been exceeded (lipotoxicity).
- Non-mathematical suggestions for adding the parameters of dynamics and limits of the size of TAG stores in various body compartments to the models.

Problem outlining, 5

- What is the quantitative relationships between accumulation of fat, its determinants, and the individual limits of expandability?
- Is it necessary to define different expandability characteristics for different adipose depots?
- Can the individual differences and changes over time in the relative size of the various adipose depots be defined as quantitative expandability characteristics?

Problem outlining, 6

- Are the limits of expandability a fixed value or is it dynamic in the sense that there is an increasing resistance toward expansion the greater the depots already are?
- Can the expansion of the fat depots be considered analogous to inflation of a balloon?
- Can the expandability of the individual adipose depots be broken down to determinants of adipocyte number and size?

Mathematical imaginations

- Can the limits of expandability of the adipose depots be defined as a energy storage capacity and integrated as an attractor in the models for body weight regulation?
- Can the model allow for individual differences and changes over time of this attractor?
- Can the model incorporate feedbacks from the expansion process, including approaching the maximum or break point, to the determinants of expansion?

NICOLAUS STENONIVS



Pulchra sunt, quae videntur
Pulchriora quae sciuntur
Longe pulcherrima quae ignorantur

Danish scientist born 1638, working in various locations in Europe, mainly in Florence, supported by the Medici family
Until his 36th year (1674) he described:

- the structure of the brain,
- the existence of exocrine glands,
- the heart as a muscle pump,
- the skeletal muscle structure-function relation explaining contraction,
- and many other things in geology, palaeontology and crystallography

Disregarded all prevailing beliefs, ideas and expectations, considered them as prejudice, made observation and logical inferences on their basis. We may need help from a new Nicolaus Stenonius to solve the enigmas of obesity and thereby lift the burden it puts on the people of the world.

I thank my collaborators, especially Edmund Christiansen and Antonio Vidal-Puig, the NIMBioS – & Diana, Kevin and Steve – for the invitation and you for your attention!

Beautiful is what we see
More beautiful is what we know
Most beautiful is what we do not know