Obesity-the growing epidemic

PROF TESS VAN DER MERWE

FCP (SA); PhD
Endocrinologist

Honorary Professor and
Researcher
University of Pretoria

CEO CEMMS(SA)
Chair SASSO
The 12 pillars of understanding
1. Recognizing the magnitude of the disease: Epidemiology
10 Billion
is the estimated size of the global population by 2015

900 Million
People worldwide are hungry
2 billion have micronutrient deficiencies and

2 billion are overweight or obese
SA statistics

46% of the world’s 600 million obese people are from the developing world

- 50% of SA’s will die before 65y from chronic disease
- 15% of SA’s buy monthly “vitamins” to aid “weight loss”
- 40% of SA’s buy OTC’s for their weight related co morbidities.

Age-standardised regional and national estimates of the prevalence of and obesity men and women for 2013, for 188 countries and 21 GBD regions
Lancet 2014: online 60460-8
South Africa is becoming a fatter nation

<table>
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<td>1998 – SADHS*</td>
<td>24.8</td>
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<td>2013 – SANHANES*</td>
<td>27.0</td>
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* South African Demographic & Health Survey
* South African National Health & Nutrition Examination Survey
Non-communicable diseases
Injuries
Communicable diseases

NCD’S STRIKING EARLIER
Percentage of total deaths by age group, 2013

Financial Mail, Dec 2014
NCD’S STRIKING EARLIER

Percentage of total deaths by age group, 2013

Financial Mail Dec 2014
2. Health Economic Burden of the disease
Each 1-point increase in BMI yields a 4% increase in medical costs and a 7% increase in pharmaceutical costs (Wang et al).

Direct medical costs are 42% higher among obese adults compared to their normal weight counterparts.

Indirect costs due to obesity, including absenteeism and reduced productivity whilst working has been shown to exceed the direct costs.

Obesity is now responsible for >9% of all medical expenditures,

Combined value of these costs > R60 000/year/capita.
The Medical Care Costs of Adult Obesity: Per Case and Aggregate for the USA
3. Genetic and Epigenetic control of Obesity
Both baseline BMI and weight gain are genetically determined, and they are each regulated by a different set of genes.

While one set of genes may determine how big you are, other genes may determine how large you can get.

Rare to find MZ twins that are discordant for weight. Clear evidence for the well-known fact that body weight is one of the most heritable complex traits found in man. Only marginally less heritable than height.
Individuals with single defective gene

~60 Million obese individuals

~60 Million overweight individuals

~60 Million normal weight individuals

Genetic Obesity (5%?)

Strong Predisposition

Slight Predisposition

Genetically resistant

Bouchard, Rankinen. Ob Management. 2005
High energy intake & low energy expenditure

Normal energy intake and expenditure

Single gene mutation

Polymorphic Genetic susceptibility

Normal genetic background

Body Mass Index (kg/m²)
• List of studies demonstrating trans generational inheritance of metabolic disease

• Genetic modification: change in base sequence of DNA
• Epigenetic modification: chemical modification to DNA
• Epigenetic marks are heritable through mitotic cell division by either methylation or acetylation

Genome is largely stable but epi-genome has the potential to be irreversibly modified by exposure to a range of nutritional and environmental factors
Transgenerational inheritance of metabolic disease

F0
Conventional Inheritance
Pregnant Female

F1
Intergenerational Inheritance
Pregnant Female

F2
Transgenerational Inheritance
Pregnant Female

F3
Generation
4. Understand the complex Aetiology

- Neuropeptides
- Gut peptides
- Stress axis/cortisol
- Biological factors
- Inflammation-cytokines
- Adipogenesis
- Endocrinopathies
- Medication
- Gender related
- Social/economic
BRAINS GREW BIGGER—and hence more energetically demanding—over time. The modern human brain accounts for 10 to 12 percent more of the body’s resting energy requirements than the average australopithecine brain did.
ENVIRONMENT

THE BIG 2:
- Increased energy intake
- Reduced physical activity

OTHER FACTORS:
- Radiation/chemotherapy
- Longer time spent awake
- Increased age of mothers at first birth
- Reduced variability in seasonal ambient temperature
Metabolic disorders

OBESITY

Chronodisruption

Energy Balance

Activity/Wakefulness
Feeding
Energy Intake and Storage

High Insulin Sensitivity
- Liver: Glycogen synthesis, Glycolysis
- White Adipose Tissue: Lipogenesis, Adiponectin
- Pancreas: Insulin secretion

Rest/Sleep Fasting
Energy Expenditure

Insulin Resistance
- Liver: Glycogenolysis, Gluconeogenesis
- White Adipose Tissue: Lipolysis, Leptin
- Pancreas: Glucagon secretion

Body Weight

Activity/Wakefulness
Feeding

Insulin Resistance
- Liver: Glycogenolysis, Gluconeogenesis
- White Adipose Tissue: Lipolysis, Leptin
- Pancreas: Glucagon secretion

Rest/Sleep Fasting

High Insulin Sensitivity
- Liver: Glycogen synthesis, Glycolysis
- White Adipose Tissue: Lipogenesis, Adiponectin
- Pancreas: Insulin secretion
Percentage of Households having both Underweight and Overweight members (7 Countries)

Vietnam
China
Kyrgyzstan
Indonesia
Russia
Brazil
U.S.

Lower GNP
Higher GNP

Caballero B. NEJM April 14, 2005
Infant weight and risk of IR and Diabetes

- Small for gestational age
- Large for gestational age
- Premature infants
- Catch-up growth of low birth weight babies
Barker hypothesis: Lifecycle - the proposed causal links

- **Woman Malnourished**
  - Pregnancy Low Gain
  - Elderly Malnourished

- **Baby Low Birth Weight**
  - Inadequate foetal nutrition
  - Rapid Growth
  - Inadequate catch up growth
  - Visceral obesity, Hypertension, Diabetes

- **Child Stunted**
  - Adolescent Stunted
The Influence of Poverty on Obesity (Body Mass Index >30 kg/m$^2$)

The Influence of Education on Obesity (Body Mass Index >30 kg/m$^2$)
5. Obese Children = Obese Adults
22% of children aged 1y-9y at BMI > 25
25-28% of adolescent girls obese

National Representative Study:

Overweight: 20.1 % Urban Children
15.8 % Tribal children
10.8% Children on farms
GIRLS – SA decline in fitness

GIRLS - SA decline in fitness

Thrusts - 2kg medicine ball from chest

3x horizontal jumps (meters)

Height

Weight

2014
1985
BOYS – SA decline in fitness

BOYS - SA decline in fitness

- **Thrusts - 2kg medicine ball from chest**
  - 2014: 9.8 meters
  - 1985: 6.9 meters

- **3x horizontal jumps (meters)**
  - 2014: 6.4 meters
  - 1985: 6.9 meters

- **Height**
  - 2014: 1.64 meters
  - 1985: 1.6 meters

- **Weight**
  - 2014: 59.4 kg
  - 1985: 57.5 kg

The graph shows a comparison between 2014 and 1985 for various fitness components, indicating a decline in fitness over this period.
Childhood obesity is a strong predictor of adult obesity, particularly where both parents are obese.

Prevalence of Metabolic Syndrome in adults:
Childhood obesity: 28%
Without childhood obesity: < 10%

<table>
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<th>Age group</th>
<th>Neither parent obese</th>
<th>At least one parent obese</th>
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<td>3-5 years</td>
<td>24%</td>
<td>62%</td>
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<tr>
<td>10-14 years</td>
<td>64%</td>
<td>79%</td>
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</table>
6. The complexity of appetite regulation
Schematic integration of the different levels of food intake and energy balance regulation
### Key points

- Obesity results from genetic and environmental factors that interfere with the action of brain and peripheral networks involved in regulating energy balance.
- The control of energy expenditure is, in part, exerted on the activity of brown adipose tissue, which might have a considerable thermogenic effect in the body.
- The controls of energy intake and expenditure are insured by interrelated cortical executive, reward and autonomic circuits in the brain.
- The dopamine mesolimbic circuit and the opioid, endocannabinoid and melanocortin systems are key central nervous system elements in energy homeostasis.
- Leptin and ghrelin are peripheral homeostatic hormones that signal to the brain to provide information on energy balance and nutritional status.
7. The difficulty in maintaining weight loss

The great thing in this world is not so much where we are, but in what direction we are moving.

Oliver Wendell Holmes (1809-1894)
How Habits Form

We use three steps to learn and lock in habits: explore a new behavior, form a habit, then imprint it into the brain (colored numbers). Although scientists have not refined all the details, the striatum (center) coordinates each step. Even though we seem to carry out habits “without thinking,” the infralimbic cortex (bottom right) still monitors what we are doing.

1. New behavior explored: The prefrontal cortex communicates with the striatum, and the striatum communicates with the midbrain, where dopamine aids learning and assigns value to goals. These circuits (solid and dashed lines) form positive feedback loops, which help us figure out what does and does not work in the behavior.

2. Habit forms: As we repeat a behavior, a feedback loop between the sensorimotor cortex and the striatum becomes strongly engaged, which helps us stamp routines into a single unit, or chunk, of brain activity. The chunk partly resides in the striatum and relies on dopamine input from the midbrain.

3. Habit imprinted and permitted: Once a habit is stored as a chunk of actions, the infralimbic cortex seems to help the striatum further imprint the habit as a semipermanent brain activity. Aided by dopamine, the infralimbic cortex also seems to control when to allow us to engage in a habit; shutting down this region can suppress deeply ingrained routines.
Acting without Thinking

Tests on rats revealed that the brain treats a habit as a single unit of behavior. The rats learned to run down a T-maze and turn left or right toward a reward, depending on an instruction sound. During early runs (first colored T), activity in the brain’s striatum was high (yellow and red) most of the time. As a habit formed (second T), activity quieted (green and blue) except when the rat had to decide to turn or to drink. Once a habit set in (third T), activity was high only at the start and finish, marking one unit of behavior.
Homeostatic and Non-homeostatic Pathways Involved in the Control of Food Intake and Energy Balance
**Hedonic obesity**

- Elevated body weight above set-point
- Temporarily elevated body weight
- Metabolic signal to reduce food intake
- "Adaptive changes" in weight
- Energy expenditure

**Metabolic obesity**

- New set-point body weight
- Metabolic signal to increase food intake
- "Adaptive changes" in weight
- Energy expenditure

Hedonic mechanisms: driven by "pleasure", i.e., eating to satisfy reward/punishment balance

Homeostatic circuits: to defend set-point body weight, i.e., metabolic regulation to achieve energy balance
Dieting and weight cycling as risk factors for cardiometabolic diseases: who is really at risk?
How dieting makes the lean fatter: from a perspective of body composition autoregulation through adipostats and proteinstats awaiting discovery
8. Understanding Insulin resistance
Metabolic Syndrome

Body Size
- ↑ BMI
- ↑ Central Adiposity

Hyper insulinemia

Glucose Metabolism
- ± Glucose intolerance

Uric Acid Metabolism
- ↑ Uric acid
- ↓ Urinary uric acid clearance

Dyslipidemia
- ↑ TG
- ↑ PP lipemia
- ↓ HDL-C
- ↓ PHLA
- Small, dense LDL

Hemodynamic
- ↑ SNS activity
- ↑ Na retention
- Hypertension

Novel Risk Factors
- ↑ CRP
- ↑ PAI-1
- ↑ Fibrinogen
- NASH
- PCOD

CORONARY HEART DISEASE

Adapted from Reaven G. Drugs. 1999;58 (suppl):19-20
INSULIN DOSE RESPONSE CURVES FOR STIMULATION OF GLUTOSE UPTAKE, SUPPRESSION OF GLUTOSE PRODUCTION AND SUPPRESSION OF LIPOLYSIS

![Graph showing various curves for glucose uptake, glucose production, and lipolysis response to different levels of serum insulin.](image)

- **Glucose Uptake**
- **Glucose Production**
- **Lipolysis**

**EC₅₀** indicates the concentration of serum insulin at which half of the maximal effect is observed for glucose production. The graph shows the physiologic range and the clamp level for serum insulin concentrations.

**Percent maximal effect** on the vertical axis ranges from 0% to 100%, while the serum insulin concentrations are on a log scale from 5 to 500 µU/ml.
Mechanisms of Increased Ectopic Lipid Deposition in the Liver and Skeletal Muscle

Energy intake > Energy expenditure

↑Fatty acid flux
Defects in adipocyte fatty acid metabolism

Skeletal muscle
Liver

Ectopic lipid deposition

Defects in mitochondrial metabolism, biogenesis, or both, leading to decreased fat oxidation
Normal intracellular FA homeostasis

Obesity – impaired FA homeostasis with β cell death
HFD-induced leptin resistance and obesity

Short-term HFD-feeding

Chronic HFD-feeding
Regulation of Obesity-Related Insulin Resistance with Gut Anti-inflammatory Agents

**Highlights**

- High-fat diet induces low-grade bowel inflammatory changes in resident immune cells
- Altered gut immunity in obesity contributes to obesity-related insulin resistance
- Gut immunity alters gut barrier, fat inflammation, and oral tolerance in obesity
- Targeting gut inflammation is a novel treatment approach for metabolic disease
9. The principles of Nutrition

Effect of Allowing Choice of Diet on Weight Loss
Defective Biology

Obesity Predisposition

Adapted from Ravussin and Bouchard, 2000
Annual fast food

Burger and chicken transactions in South Africa

Euromonitor Report 2012
INFOGRAPHIC: WHAT’S SA’S MOST SUGARY DRINK?

We gathered a few popular drinks from our canteen’s refrigerator to check how much sugar each one contains. The results were surprising. Even ‘healthier’ drinks such as flavoured mineral water and drinking yogurt contain a large amount of sugar.
Drinking our kilojoules

Sweetened cool drinks are a major contributor to our high sugar intake. Each soft drink contains up to 35g of sugar.

By 2012 South Africans were drinking 260 cans of Coke per person per year, that’s almost three times the global average. *Coca-Cola Annual Report.*

One or more soft drink per day increases risk of diabetes by 26%. Sugar also increases risk for obesity. Risk increases when sugar is consumed in the form of a sugar-sweetened beverages.

Sugar limits


Up to 100g+: The amount of sugar some adults have per day. This includes sugar added to foods such as cereal and tea as well as what is already in processed foods.

How much sugar is in a …

- 500ml fizzy cool drink = 55g (13sp)
- 250ml low fat drinking yoghurt = 20g (5sp)
- 250ml flavoured water = 20g (4.8sp)
- 500ml Energade or Vitamin water = 25g (6.2sp)
- 250ml energy drink = 27.5g (6.8sp)
- 330ml ice tea = 29g (6.2sp)
- 150ml low fat flavoured yoghurt = 8.7g (2sp)
- 250ml can of fizzy drink = 36g (8.5sp)
The Relationship between Energy Density (Kcal/100g) and Energy Cost ($/100 kcal) in Nine Major Food Groups
10. The Role of Physical Activity
Sedentary living

A typical day

It’s not difficult to spend 90% of your day sitting down: from breakfast at the table, to the commute to work, a day in the office, the drive home, dinner time, and a few hours in front of the TV, much of modern living happens in a seated position. ‘Sitting is the new smoking’ as they say, and too much chair time can be detrimental to your health, particularly if you are prone to metabolic illnesses like diabetes.

Discovery Vitality
Remarkable genetic variability in response to training and exercise

While factors such as baseline fitness, age, sex, weight, or ethnicity, each explain only around 2-5% of the variability to exercise response, familial aggregation can explain around 50% of the variability.

This has important implication for the risk of weight gain

Being “genetically-programmed” for high levels of spontaneous physical activity (e.g. fidgeting) and having genes that allow the body to rapidly adapt to and benefit from regular exercise will make you much less likely to gain weight than if your genetic program reads “sedentariness”
Changes in Levels of Physical Activity and Time Spent in Sedentary Behaviour in the US

TV
Social contact
Reading
Exercise
PC

Total energy expenditure has clearly decreased worldwide over the last 20 years (National Statistics 2002)
### Fit for Life?

The Number of Europeans who never exercise or play sport:

<table>
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<th>Country</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Portugal</td>
<td>66%</td>
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<tr>
<td>Italy</td>
<td>58%</td>
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<tr>
<td>Spain</td>
<td>47%</td>
</tr>
<tr>
<td>Germany</td>
<td>36%</td>
</tr>
<tr>
<td>France</td>
<td>35%</td>
</tr>
<tr>
<td>Britain</td>
<td>31%</td>
</tr>
<tr>
<td>Finland</td>
<td>13%</td>
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Trends in People Inactive or Insufficiently Active in the State of Sao Paulo, Brazil during the Years 2002, 2003, 2006 and 2008

Trends in Physical Activity in the State of Sao Paulo, Brazil during the Years 2002, 2003, 2006 and 2008
<table>
<thead>
<tr>
<th>Weight</th>
<th>24h energy expenditure (kcal per day)</th>
<th>Energy stores (kcal)</th>
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<tbody>
<tr>
<td>77kg man</td>
<td>2657</td>
<td>17kg</td>
</tr>
<tr>
<td>70kg man</td>
<td>2535</td>
<td>10kg</td>
</tr>
<tr>
<td>Difference</td>
<td>122</td>
<td>50,000 kcal</td>
</tr>
<tr>
<td>Walking for 30min /day</td>
<td>150</td>
<td></td>
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<tr>
<td>Chocolate biscuit / day</td>
<td>150</td>
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Characteristics of individuals maintaining a weight loss of at least 13.6 kg (McGiure et al)

**Body weight loss** 13.6kg

**Period of maintenance** 5.7 years

**Relative fat intake** 25% of total energy intake

**Physical activity** 11 847KJ (or 2820 cal)/week
Changes that occur with endurance training

Cardiovascular and whole-body
- Increased cardiac output, and ability to increase this during exercise
- Improved respiratory function
- Increased lean body mass (mainly muscle bulk)
- Decreased body fat
- Increased bone strength

Structural changes in muscle
- Increased density of capillaries
- Increased number of mitochondria
- Increased size of mitochondria
- Increased myoglobin concentration

Metabolic changes in muscle
- Increased expression of GLUT4
- Increased sensitivity to insulin
- Increased activity of lipoprotein lipase
- Increased activity of oxidative enzymes in mitochondria (tricarboxylic acid cycle and β-oxidation)
- Increased glycogen synthase activity
Excess postexercise oxygen consumption (EPOC) resulting from 20, 50 and 80 minutes of treadmill exercise at 30, 50 and 70% VO$_2$ max. Adapted from Gore and Withers (1990).
Appetite control and energy balance: impact of exercise

Caloric intake as a function of level of physical activity at work, in an industrial male population in West Bengal. From Mayer et al. (1956)
To have a purpose that is worthwhile, and that is steadily being accomplished, that is one of the secrets of a life that is worth living.

Herbert Casson (1869-1951)
Stepped Care Approach to Obesity Management

- Hypocaloric diets
  - Lifestyle intervention BMI 25-30
- Pharmacotherapy BMI 27-35
- Roux-N-Y Gastric bypass for DM/PCOD BMI > 30
- Roux-N-Y Gastric Bypass BMI > 35
- Biliopancreatic diversion BMI > 52

Degree of Long-Term Weight loss

Treatment Intensity
Several pharmacological approaches used to control hyperglycaemia in type 2 Diabetes, with a focus on the drugs’ effects on bodyweight.
DUODENUM
- Cholecystokinin
- Gall bladder contraction
- Gastrointestinal motility
- Pancreatic endocrine secretion
  - Secretin
- Pancreatic endocrine secretion
  - GIP
  - Incretin activity
  - Motilin
  - Gastrointestinal motility

STOMACH
- Ghrelin
  - Hunger
- Growth hormone release
- Gastrin
  - Acid secretion

PANCREAS
- Insulin and glucagon
  - Glucose homeostasis
- Pancreatic polypeptide
  - Gastric motility
  - Satiation
- Amylin
  - Glucose homeostasis
  - Gastric motility

INTESTINES
- GLP-1
- Incretin activity
  - Satiation
- GLP-2
  - Gastrointestinal motility and growth
- Oxyntomodulin
  - Satiation
  - Acid secretion
- PYY
  - Satiation
  - 3-34
  - Satiation
The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes
Duodenal energy sensing regulates hepatic glucose output
*Nature 21: 5; May 2015*
MECHANISMS OF BARIATRIC SURGERY – KEY FOR NOVEL THERAPIES?

Surgical Procedures

Biliopancreatic Diversion with Duodenal Switch

Gastric pouch
Duodenum
Intestines
Roux limb

Sleeve Gastrectomy

Gastric “sleeve”
Pylorus

Adjustable Gastric Band

Tube to carry fluid
Gastric band
Subcutaneous injection port
## Tallies up to the end of July 2015

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<th>HOSPITAL</th>
<th>SURGEON</th>
<th>TOTALS</th>
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<td>George Mediclinic</td>
<td>Dr. Folscher</td>
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<td>Durbanville Mediclinic</td>
<td>Dr. Swanepoel</td>
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</table>
Conclusions

‘Do you suppose rapid eye movement counts as exercise?’
Health Cost Saving

- 5% weight reduction:
  - BMI 30: R700/y
  - BMI 35: R5280/y
  - BMI 40: R20137/y

- To save $10,000,000/y
- Need to lower BMI by 5% in 14,500 people living with BMI at 30
- Need to lower BMI by 5% in only 100 people living with BMI at 40
OBESITY is very complex, and requires understanding

More needs to be done to debunk the myths and stereotypes that shape the attitudes of health professionals.
Prevalence of overweight and obesity
Self-assessment vs. reality

%
70
60
50
40
30
20
10
0

Females

%
70
60
50
40
30
20
10
0

Males

self-assessment
reality

2002

Self-assessment vs. reality

Prevalence of overweight and obesity

%