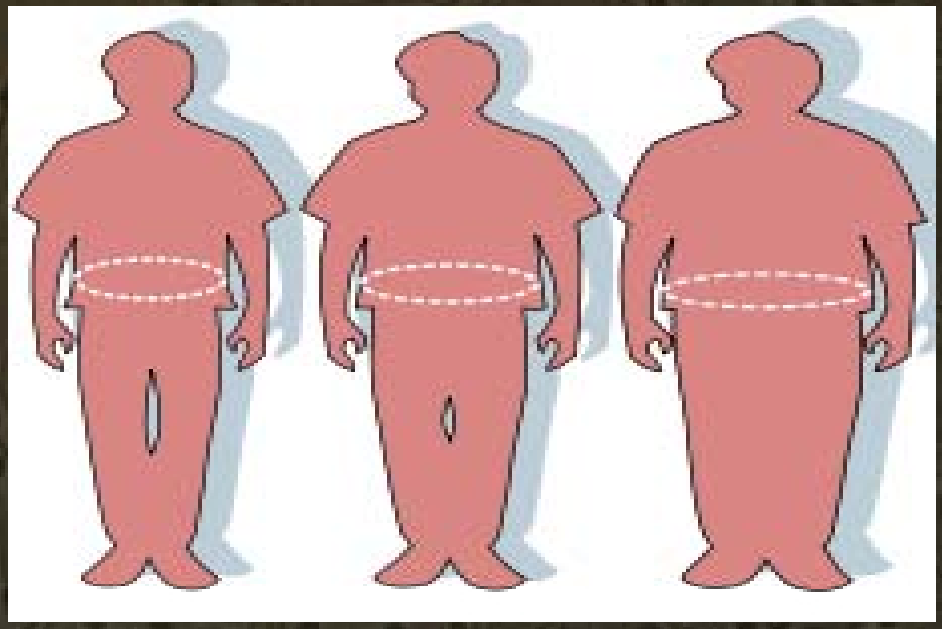
THE TUREK CLINIC

The Effect *of* BMI, Body Fat *and* Age *on* Semen Parameters



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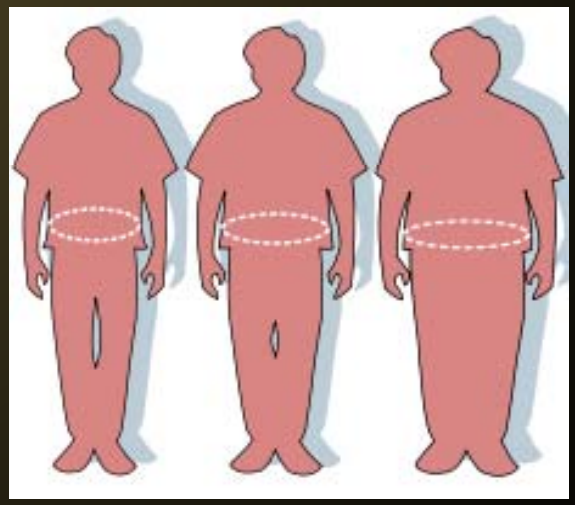
Learning Objectives

At the conclusion of this presentation participants should be able to:

- Delineate known correlations of semen quality with BMI.
- Explain how body fat might influence semen quality.
- Describe what happens to semen quality with age.
- Discuss changes in sperm genetics with advanced paternal age.

Obesity and Semen Quality

- Obesity is typically measured as **Body Mass Index (BMI)** which relates weight to height
- **Body fat** is typically measured by waist circumference
- **BMI** is a reliable (but not the most accurate) indicator of "fatness"
- **Ideal BMI** for both men and women is **20-25**
- **Overweight** is BMI 26-30
- **Obese** is BMI>30
- **Severe obesity** is BMI>35
- **Morbid obesity** is BMI>40
- **Super obesity** is BMI>45



BMI *and* Male Infertility

- **Obese men have more trouble achieving pregnancies.**

Danish cohort study of 26,303 planned pregnancies.
Adjusting for partner BMI, coital frequency, ages and smoking habits **Nguyen et al. Hum Reprod.2007, 22: 2488**

BMI	OR of infertility	(CI)
<25.5	1	
25-30	1.2	1.04-1.38
30-35	1.36	1.13-1.63

- **Obese men have lower sperm counts and motilities.**

Utah cohort study of 526 infertile men:

BMI <25 5.3% oligospermia
BMI 25-30 9.2% oligospermia
BMI >30 15.6% oligospermia

Hammoud et al Fert Steril. Epub Jan 2008

BMI *and* Semen Quality

Meta-analyses of 14-21 studies; n=10-13k subjects
General population and infertile subjects

In a nutshell:

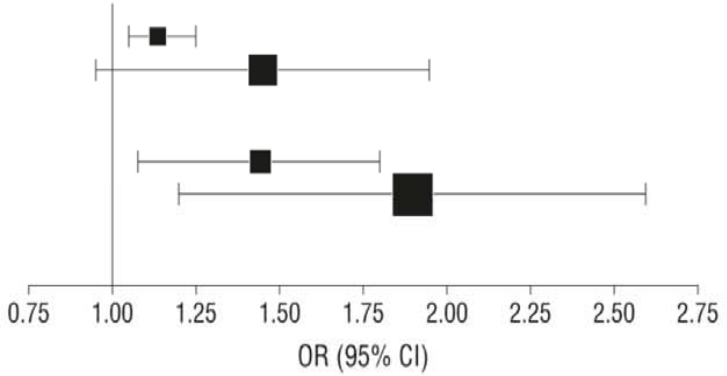
- Obese men are **42%** more likely to have **oligospermia**
- Obese men are **81%** more likely to have **azoospermia**
- For every **20 lb** increase in weight, **10%** increase in the chance of infertility

Sermondade et al. Arch Int Med. 2012 172: 440-442
Sermondade et al. Hum Reprod Update. Dec 2012 Dec Epub

BMI *and* Semen Quality

Meta-analyses of 21 studies; n=13k subjects
General population and infertile subjects

	No. of Studies	No. of Events/Total Patients: Controls	No. of Events/Total Patients: Cases	OR (95% CI)	*P* Value*
Normal weight vs overweight					
Oligospermia	15	1242/5179	854/3340	1.11 (1.01-1.20)	.15
Azoospermia	9	100/3902	111/2340	1.39 (0.98-1.97)	
Normal weight vs obese					
Oligospermia	15	1242/5179	370/1143	1.42 (1.12-1.79)	.28
Azoospermia	10	100/3902	47/679	1.81 (1.23-2.66)	



Sermondade et al. Arch Int Med. 2012 172: 440-442

BMI *and* Semen Quality

On the other hand…

- Meta-analysis of 31 studies
- 5 Suitable for pooling
- "No evidence for a relationship between BMI and sperm concentration or total sperm count"
- Strong evidence of a negative relationship of **testosterone** with **increased BMI**.

MacDonald et al. Hum Reprod Update 2010, 16: 293-311

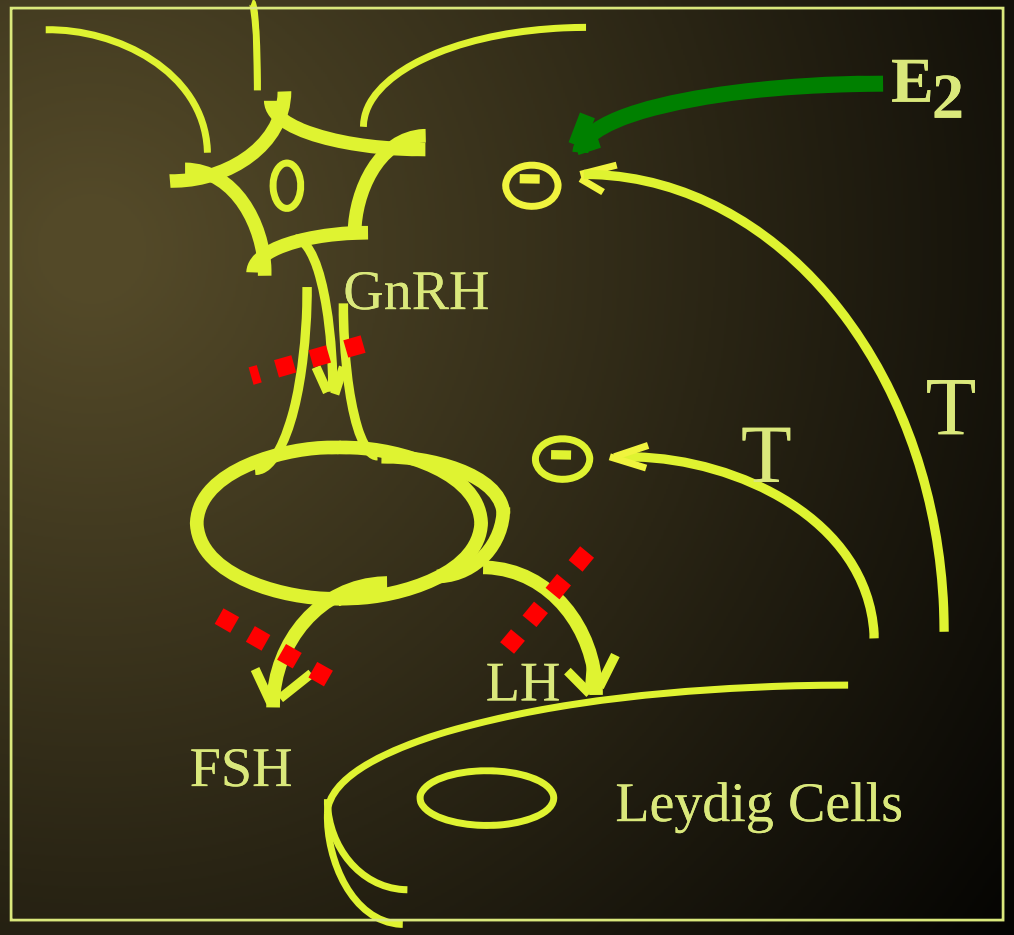
Body Fat *and* Semen Quality

- N=81 infertile subjects
- Semen parameters; hormones and waist, hip size
- Waist circumference correlated with:
  - Sperm count
  - Progressively motile sperm count
  - Total motile sperm count

Fejes et al. Andrologia 2005, 37: 155-9

BMI, Obesity and Semen Quality: Mechanism

- **Co-morbid conditions-"Metabolic syndrome"**
  - Hyperlipidemia
  - Hypertension
  - Heart disease
  - Diabetes
- **Hyperestrogenism**
- **Body stress**



Stress Reduction Kit

Directions:

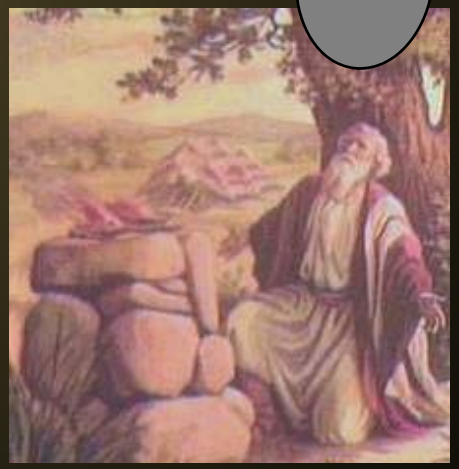
1. Place kit on FIRM surface.
2. Follow directions in circle of kit.
3. Repeat step 2 as necessary, or until unconscious.
4. If unconscious, cease stress reduction activity.

When Does Paternity End?

73

72

99



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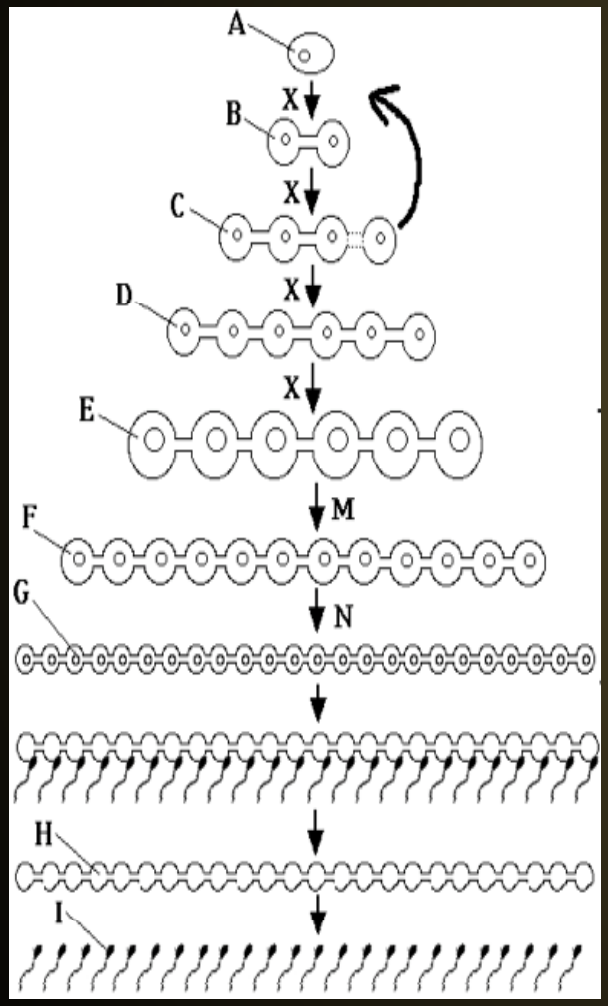
Courtesy: Dr. Saleh Binsaleh

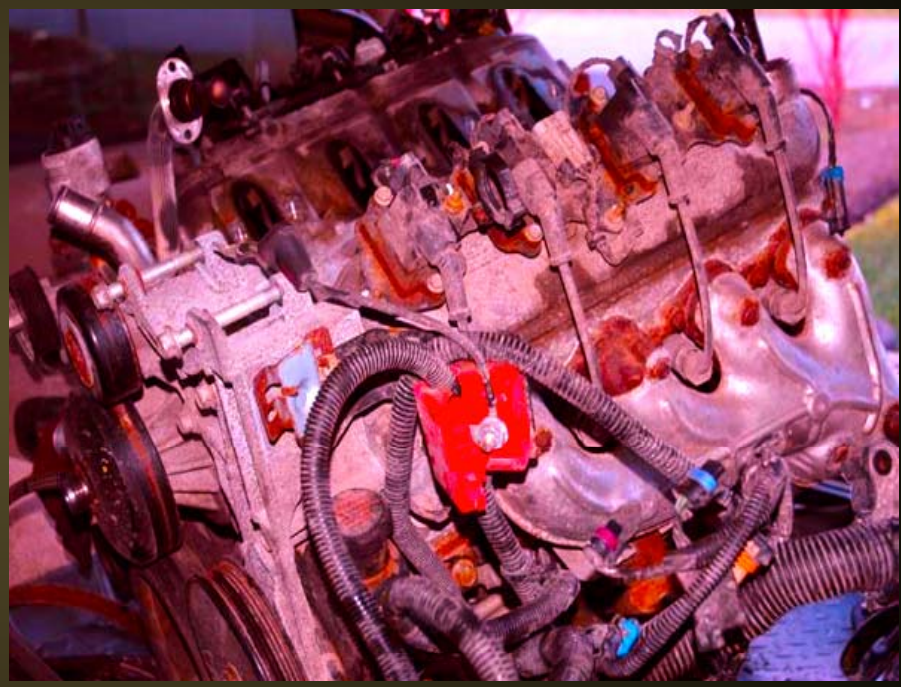
Think of spermatogenesis as an engine..



By puberty: **30** spermatogonial divisions
After puberty: **23** divisions/year
By age 70: **1288** divisions

Wiener-Megnazi et al, Asian J Androl. 2012; 14: 269

What happens when engines get old?



They don’t run as smoothly, or at all.

Paternal Age *and* Semen Quality

Lower ejaculate volume. Changes in prostate protein and water content
Decreased fructose from SV
Sperm motility falls (gradually)
Concentration changes harder to show

Kuhnert. Hum Reprod Upd, 2004; 10:327-339
Wyrobek AJ. PNAS, 2006; 103:9601

Paternal Age *and* Semen Quality

Study	Semen Volume (mL)		Sperm Density (Millions/mL)		Sperm Motility (%)	
	Younger	Older	Younger	Older	Younger	Older
Schwartz 1982	3.2	3.1	77	81	70*	65
Nieschlag 1982	----	----	78*	120	68*	50

Note: * indicates that difference was statistically significant

Schwartz et al. Fertil Steril. 1983, 39: 530
Neischlag et al. JCEM. 1982, 55:576

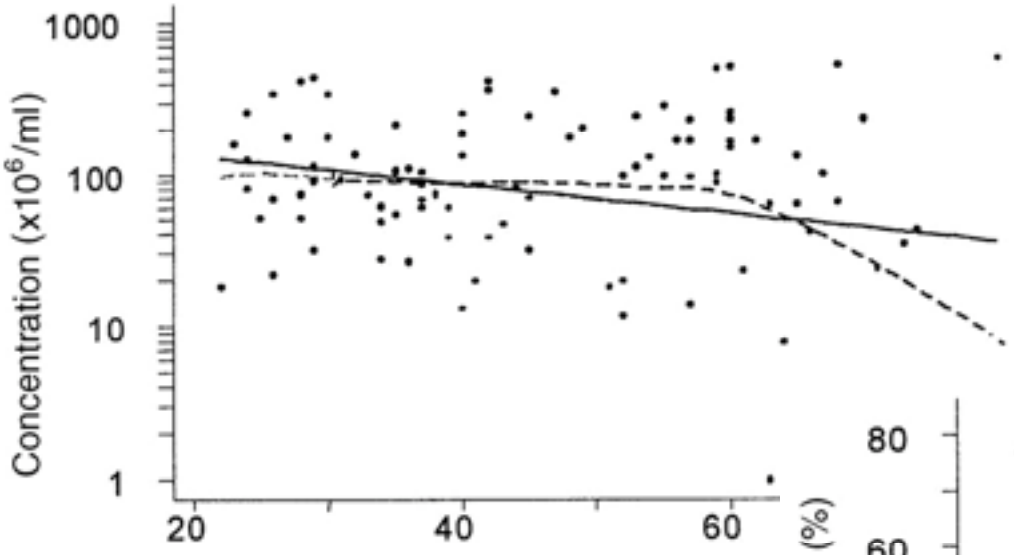
Paternal Age and Semen Quality

- N=97 non-smoking men
- Non-clinical, convenience sample
- Age range 22 to 80 years
- Co-variates: lifestyle, profession, diet, medical conditions

Parameter	Change with Age
Volume	0.03 mL decrease/year
Concentration	No significant change
Motility	0.7% decrease/year

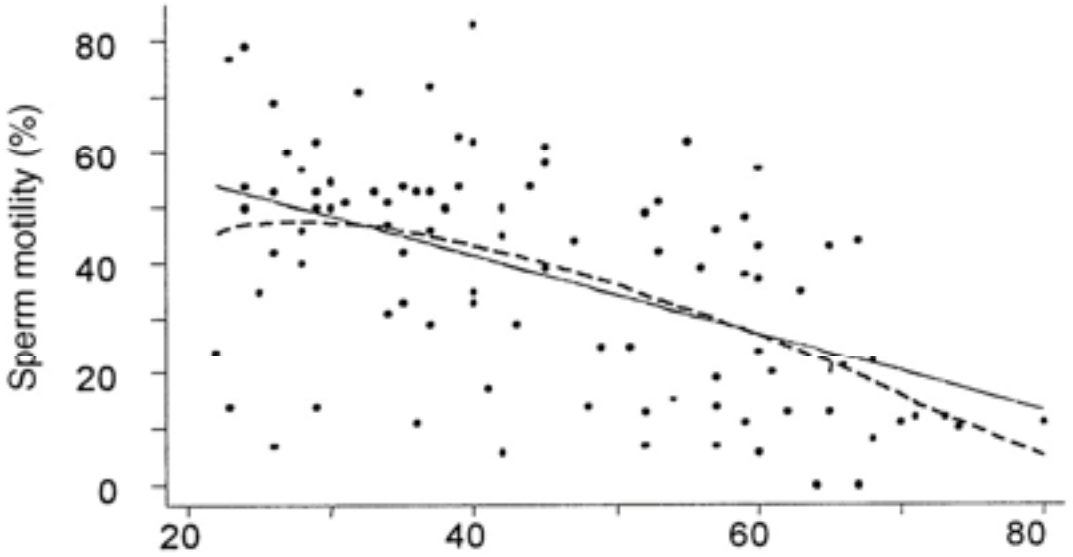
Eskenazi et al. Hum Reprod. 2003. 18: 447-54

Paternal Age *and* Semen Quality



Concentration

Motility



Eskenazi et al. Hum Reprod. 2003. 18: 447-54

Quality Control "Issues"

- **Single gene** or **point mutations** in human germ line cells are common; increase with paternal age.

- Thought to stem from **replication errors** during meiosis

- **New**: These mutations are **not random** (from poor quality control), but demonstrate **"allelic skewing."**

- **New:** Paternal age effect mutations follow a **"selfish" pathway** that favors clonal proliferation of cells and leads to specific phenotypes in offspring.

Goriely et al, Nat Genet. 2009, 41: 1247
Goriely and Wilkie, Am J Hum Genet. 2012, 90: 175

Quality control "Issues"

- Studied **spermatocytic seminomas**.
- Examined mutations typically found in offspring of older fathers (**sentinel mutations**).
- Massive parallel sequencing of sentinel mutations, FGFR2, FGFR3, RET, signal transduction pathways, pathologically activated genes.
- ***Found increased sentinel mutations in these tumors.***
- Proposed that common **"selfish"** mutations **"hijack"** the pathway and lead to both:
  a) tumors
  b) diseases in offspring

- Sperm produced are in **"evolutionary conflict:"** good for production but bad for species.

Goriely et al, Nat Genet. 2009, 41: 1247
Goriely and Wilkie, Am J Hum Genet. 2012, 90: 175

Paternal Age *and* Sperm Genetics

- Chromosomal issues
  - Numerical
  - Structural
- Mutations
- DNA damage

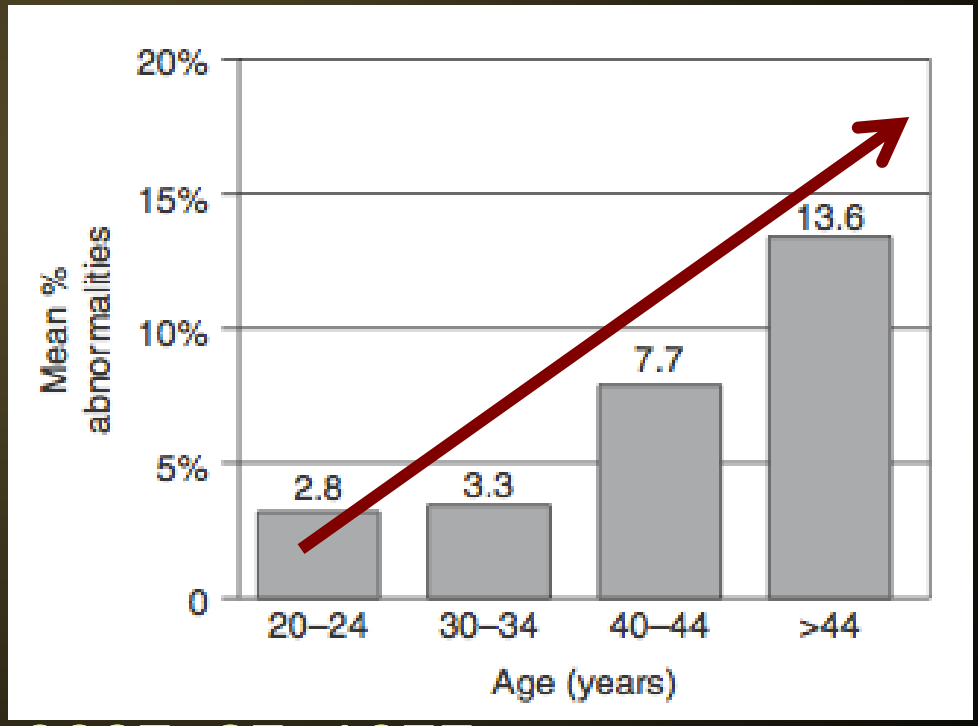
Paternal Age *and* Sperm Genetics

- Chromosomal issues: Numerical
  - Aneuploidy occurs in 30-50% of all pregnancies
  - Most are lethal
  - Arise from non-disjunction during meiosis (I and II)
  - Definite increase in aneuploidy in infertile vs. fertile sperm
  - **Autosomal aneuploidy: No consensus on** whether it increases with paternal age
  - **Sex chromosomal aneuploidy and disomy**: clear evidence that it increases with paternal age (2-3x)
    - **XY diploidy** (Meiosis I) & **XX/YY diploidy** (Meiosis II)

Sloter et al. Fertil Steril. 2004; 81:925
Templado C. Cytogenet Genome Res 2005, 111:199-205.

Paternal Age *and* Sperm Genetics

- Chromosomal issues: Structural
  - Comprise **0.25%** of births
  - **Chromosomal breaks & fragments** increase with age
  - Pronounced relationship: **r=0.63**
  - Especially chromos 1 and acentric fragments
  - **Not evident** in offspring

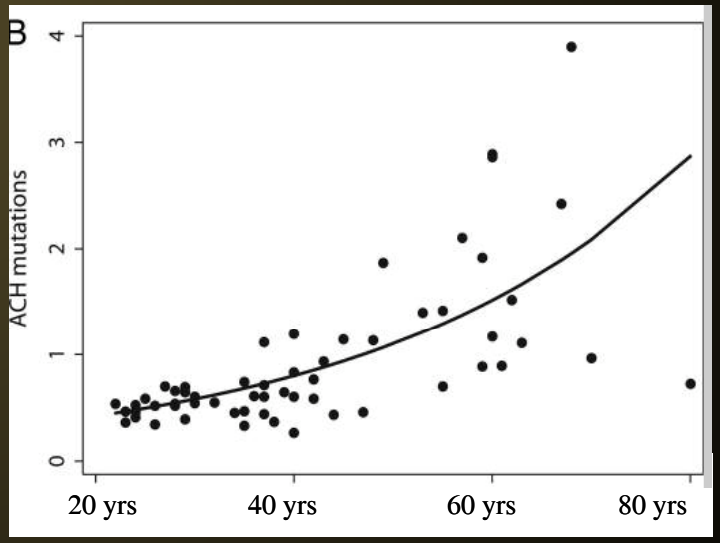


Sloter et al. Fertil Steril. 2007; 87: 1077

Martin and Rademaker. Am J Hum Genet. 1987, 41: 484

Paternal Age *and* Sperm Genetics

- Single Gene Mutations
  - **Common** in germ line cells; increase with age.
  - Replication errors during meiosis.
  - Mutations not random; **"allelic skewing."**
  - Follow a "selfish" pathway that leads to specific phenotypes in offspring.
  - Wyrobek et al. n=88 healthy, non-smoking men
  - Examined achondroplasia
  - r=.54; **Change: 2%/yr**



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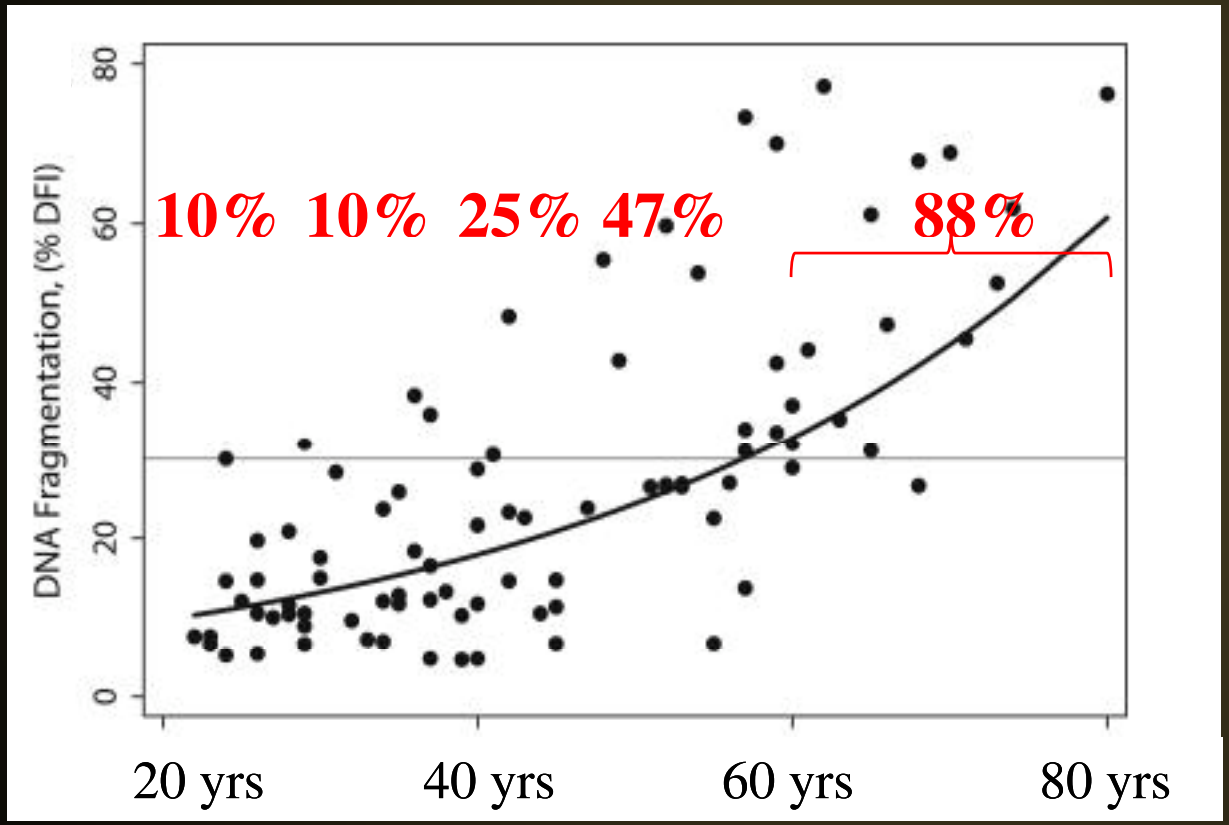
Paternal Age *and* Sperm Genetics

- Sperm DNA Fragmentation:

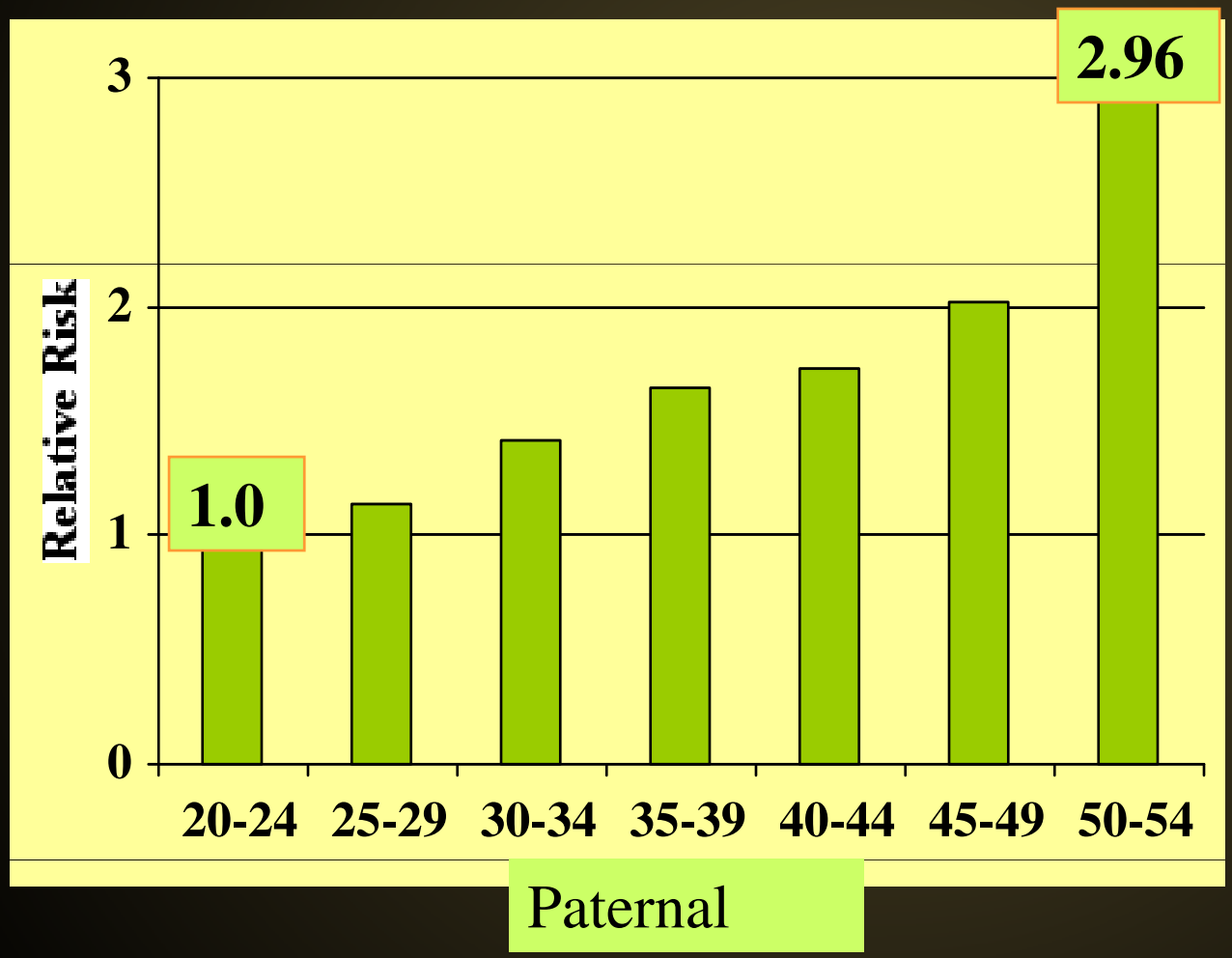


- N=88 healthy non-smokers
- r=0.72; p<0.001
- Predicted change of **3.1%/year** of age
- Associated with defective mismatch repair?

Ji et al. BMC Med. 2012, 10: 49
Wyrobek et al. PNAS, 2006; 103:9601

Paternal Age *and* Offspring

- Schizophrenia



- Israeli registry
- n=87,907 births
- Reproduced in **5** other countries

Malaspina et al. Arch Gen Psych. 2001, 58: 361

Paternal Age *and* Offspring

- Diseases-Developmental,psychiatric conditions

Condition	Relative Risk
Autism	5.7
Schizophrenia	3 - 4.6
Autism spectral disorder	1.4
Neurocognitive impairment	1.1
Dyslexia	?
Bipolar disorder	?
Alzheimer disease	?

Yatsenko and Turek. Submitted

Conclusions

BMI and body fat inversely correlate with semen quality

Ejaculate volume and sperm motility decline with paternal age

Sperm genetics and risk of offspring diseases changes with paternal age