Malthus

Malthus' Basic Theory

AN ESSAY
ON THE
PRINCIPLE OF POPULATION,
AS IT AFFECTS
THE FUTURE IMPROVEMENT OF SOCIETY
WITH REMARKS
ON THE SPECULATIONS OF MR. GODWIN,
M. CONDORCE,
AND OTHER WRITERS.

LONDON:
PRINTED FOR J. JOHNSON, IN ST. PAUL'S
CHURCH-YARD.
1798.
The Malthusian Equilibrium

Population Declines

Population Growth

Birth Rate

Death Rate

Income/ Food Availability

(subsistence income)
HMS Beagle in Sydney Harbour
January 1836
An Economic History of the World (in one slide)

Source: A Farewell to Alms
Gregory Clark
Princeton University Press 2007
### Evolution of Diabetes in Human Populations

*JV Neel’s Thrifty Gene Hypothesis*

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>1962</td>
<td>‘Thrifty gene hypothesis’</td>
<td>Increased capacity for insulin <em>secretion</em> to store energy</td>
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<tr>
<td>1982</td>
<td>Modified thrift</td>
<td><em>Selective</em> Insulin resistance (IR) in muscle sustains blood glucose in times of hunger for brain and reproductive function, but deposits fatty acids</td>
</tr>
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| 1998 | “Too simplistic”  
“Outlived its usefulness” | Neel recognized the confluence of Type 2 diabetes, abdominal obesity, dyslipidemia and hypertension, - the Metabolic syndrome - posed some particular challenges for his original idea. He concluded that the “*fine old genes*” involved in energy homeostasis were “*overwhelmed by extraneously imposed parameters of very recent origin*” |
Figure 1 | Distribution of body mass index in type 2 diabetic patients compared with non-diabetic individuals of a similar age. Individuals come from the Diabetes Audit and Research in Tayside (DARTs) study in Scotland\textsuperscript{20}. 

Thrifty or Not?
Longitudinal studies in Pima Indians, Caucasians, Mexican Americans, Creoles, Chinese, and Asian Indians have showed consistently that insulin resistance protects against weight Gain.


The same may not be true for children
Thrifty or Not?

Prevalence of Obesity Among 37,606 Diabetic and Non Diabetic U.S. (including undiagnosed) adults 20 to 74 years 1994

The relative contributions of different levels of overweight and obesity to the increased prevalence of diabetes in the United States: 1976–2004.

Edward W. Gregg, Siling J. Cheng, K.M. Mehrota Narayan, Theodore J. Thompson, David F. Williamson
Thrifty or Not?

Prevalence of Obesity Among 4126 Diabetic and Non Diabetic Pima Indian adults Aged 15-94, enrolled in a longitudinal study, 1972

DIABETES INCIDENCE IN PIMA INDIANS: CONTRIBUTIONS OF OBESITY AND PARENTAL DIABETES

WILLIAM C. KNOWLER, DAVID J. PETTITT, PETER J. SAVAGE, AND PETER H. BENNETT
Thrifty or Not?

A Requiem for the Thrifty Gene Hypothesis

1. The main evolutionary role of insulin resistance as an expressed phenotype is neither metabolic thrift nor a means to save or store energy, but a genetic and metabolic trade off.

2. In response to chronic energy insufficiency, muscle cells are “starved” of glucose in order to divert available dietary energy to the maintenance of ovarian fertility and reproduction.

3. Strong evidence in favor of this idea comes from an examination of human nutritional history, the physiology of ovulation and undernutrition and the genetics, physiology and epidemiology of the polycystic ovary syndrome.
1. Human nutritional history, demography and human evolution

2. Physiology and Epidemiology of Ovulation and Under/Over Nutrition

3. Physiology, Genetics and Epidemiology of the Polycystic Ovary Syndrome

4. PCOS and Human Evolution
   • A Left Shift in BMI/Infertility curve
   • Natural (Fertility) Selection
   • PCOS and the Evolution of Human Fertility: Fertility First?

5. PCOS and the Origins of Type 2 Diabetes and the Metabolic Syndrome
   • The Carnivore connection
   • Adaptation to agrarianism
   • Fertility Constraint
   • Three French Revolutions
Human nutritional History

Pre-Agrarian Period 3.5my BP (Hunter gatherers)
• 65% of calories animal protein and fat.
• Diet highly varied, calorie intake seasonal

Agrarian period 20000 y BP
• 35% of calories animal protein and fat.
• Diet staples, calorie intake low & seasonal

- 7 million years ago
- 6
- 5
- 4
- 3
- 2
- 1
- Today

**KEY**
- Important developments
- Pre-human primates
- Humans

**GENUS:**
- A: Australopithecus
- H: Homo

**SOURCES:** Ellen Thomas, Wesleyan Univ.; Smithsonian Institution; Washington State Univ.; Talkorigins.org; ether reporting
An Economic History of the World

![Graph showing economic history with key events such as the Malthusian Trap, Great Divergence, and Industrial Revolution marked.]
Mortality and Fertility Decline and Calories per Capita
France 1780-2000

*Les Glaneuses (The Gleaners)*
François Millet, 1857
Past and Projected Total Fertility Rate by Major Development Groups, 1950–2050
Fertile on A Famished Road
An Outline

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- The Carnivore connection
- Adaptation to agrarianism
- Fertility Constraint
- The release from constraint
Total Fertility Rate and Calories per capita per day in 167 countries (2003)
Energy Intake and Fertility in Human Populations

Figure 2: Seasonal variations in fertility in Bangladesh and Gambia.
A Focus on Ovulation and Undernutrition

WHY? Ovulation is exquisitely sensitive to the nutritional environment

- Ovarian function shows a graded response to nutritional status and energy balance
- Progression from initial suppression of the luteal and then follicular phase of the ovulatory cycle, to anovulation and reduced menstrual frequency.
The Fat and Fertility Hypothesis

Postulated, based on observations in female athletes and dancers, that a minimum amount of fat was necessary for proper female reproductive function.

Minimum fat: lean mass ratio of 17% and 22% necessary for menarche and reproductive function respectively.


Fig. 3. The minimal weight necessary for a particular height for restoration of menstrual cycles is indicated on the weight scale by the 10th percentile diagonal line of total water/body weight percent, 56.1%, as it crosses the vertical height line. For example, a 20-year-old woman whose height is 160 cm should weigh at least 46.3 kg (102 lb) before menstrual cycles would be expected to resume. Reprinted from Frisch and McArthur (1974) with permission from Science.
Reproduction is expendable at least in the short term and can be deferred until times are more favourable.

During lean times .......... Very little energy is diverted to storage of fat. Rather, calories are mobilized from fat stores in an attempt to maintain energy balance. Thus, it is energy balance not fatness per se that regulates reproductive function.

Figure 1. Partitioning of metabolic fuels by priority (Wade and Jones, 2004).

Nutrition and reproduction in women

The ESHRE Capri Workshop Group

1To whom correspondence should be addressed: P.G. Crosignani, Department of Obstetrics and Gynaecology, University of Milano, Via Como 11, 20122 Milano, Italy; E-mail: pgiorgio.crosignani@unimi.it
Leptin is an adipocyte-secreted hormone that plays a key part in energy homoeostasis.

The main role of this hormone is to signal energy availability in energy-deficient states.

Low concentrations of leptin are fully or partly responsible for starvation-induced changes in neuroendocrine axes, including low reproductive, thyroid, and insulin-like growth factor (IGF) hormones.

Leptin could act as a metabolic gate to gonadotropin secretion and observational studies suggest a critical threshold for blood leptin concentration to sustain ovulation is 2 μg/l.
The Shape of Ovulatory Infertility in Human populations

Multivariate OR and 95% CI of ovulatory disorder infertility by body mass index and distribution of body mass index

Case control design 26,125 eligible pregnancies as controls and 830 incident cases of ovulatory disorder infertility, recruited between 1989 and 19995.
# Fertile on A Famished Road

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Polycystic ovaries (PCO) are due to incomplete follicular development or to failure of ovulation.

20-30% of all women in developed countries have evidence of polycystic ovaries on abdominal ultrasound.
Polycystic Ovary Syndrome (PCOS)

PCOS is the most common cause of anovulatory infertility in developed countries.

PCOS affects 5% to 10% of all premenopausal women. A majority of women with polycystic ovaries report at least one symptom associated with the syndrome.

Polycystic Ovary Syndrome (PCOS) is diagnosed in women with at least two of the following features:

- polycystic ovaries,
- excessive secretion of androgenic hormones
- anovulatory menstrual cycles.

20-40% of women with PCOS have evidence of insulin resistance, independently of total body fat, and as a consequence a 5-10 fold risk of developing Type 2 diabetes. ~ 80% of women with Type 2 Diabetes have evidence of PCO.

The cellular and molecular mechanisms of insulin resistance in PCOS are characterised by decreased sensitivity to insulin in muscle and adipose tissue.
In obese women with PCOS insulin resistance, ovulation, menstrual regularity and fertility all improve with weight loss and physical activity and worsen with weight gain.

PCOS also occurs in women who are lean, but they tend to have an android fat distribution with abdominal obesity.

PCOS has not been well described in populations in which caloric intake and BMI are low (BMI<20).
Body fat distribution and leptin correlation in women with polycystic ovary syndrome: Endocrine and biochemical evaluation in south Indian population

**MANI RAVISHANKAR RAM,¹ PULLIANGUDI GOKULAKRISHNAN SUNDARARAMAN² and RAGHUNATHAN MALATHI**

¹Department of Genetics, Dr. ALM PG Institute of Basic Medical sciences, University of Madras, Tamilmani, Chennai,
²Department of Endocrinology, Institute of Obstetrics and Gynecology, Egmore, Chennai, Tamil Nadu, India

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Leptin concentration (ng/mL)</th>
<th>Skin-fold thickness (mm)</th>
<th>Circumference (cm)</th>
<th>Waist-to-hip ratio</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abdominal</td>
<td>Triceps</td>
<td></td>
</tr>
<tr>
<td>Normal women</td>
<td>100</td>
<td>4.08 ± 0.98</td>
<td>21.5 ± 1.49</td>
<td>12.8 ± 0.49</td>
<td>87.2 ± 0.64</td>
</tr>
<tr>
<td>Thin non-PCOS</td>
<td>20</td>
<td>2.46 ± 0.62</td>
<td>19.0 ± 1.02</td>
<td>2.8 ± 0.26</td>
<td>50.7 ± 1.28</td>
</tr>
<tr>
<td>Thin PCOS</td>
<td>20</td>
<td>15.54 ± 1.43**</td>
<td>20.0 ± 1.42</td>
<td>10.4 ± 1.27</td>
<td>54.3 ± 0.52</td>
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<td>Overweight non-PCOS</td>
<td>25</td>
<td>16.64 ± 4.48</td>
<td>30.8 ± 1.82</td>
<td>23.4 ± 1.44</td>
<td>73.7 ± 1.95</td>
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<td>Overweight PCOS</td>
<td>25</td>
<td>21.77 ± 5.38</td>
<td>32.2 ± 1.86</td>
<td>26.7 ± 1.20</td>
<td>98.4 ± 1.14</td>
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<tr>
<td>Obese non-PCOS</td>
<td>25</td>
<td>35.80 ± 1.92</td>
<td>37.2 ± 1.66</td>
<td>28.7 ± 0.72</td>
<td>120.6 ± 1.98</td>
</tr>
<tr>
<td>Obese PCOS</td>
<td>25</td>
<td>37.60 ± 1.59**</td>
<td>38.0 ± 1.52**</td>
<td>30.9 ± 0.51**</td>
<td>123.8 ± 2.16</td>
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<tr>
<td>Morbidly obese non-PCOS</td>
<td>40</td>
<td>38.84 ± 1.84</td>
<td>41.0 ± 1.14</td>
<td>32.6 ± 1.42</td>
<td>130.6 ± 1.74</td>
</tr>
<tr>
<td>Morbidly obese PCOS</td>
<td>40</td>
<td>42.6 ± 1.22**</td>
<td>43.0 ± 1.06**</td>
<td>34.8 ± 0.98**</td>
<td>134.2 ± 1.92**</td>
</tr>
</tbody>
</table>

The values are mean ± standard deviation. *P = 0.001, **P = 0.0001 is given with the statistical significance between control and polycystic ovary syndrome (PCOS)/non-polycystic ovary syndrome subjects.
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PCOS a Left Shift in Obesity/Ovulatory Infertility Curve
PCOS a Left Shift in Obesity/Ovulatory Infertility Curve
The intensity of selection by differences in fertility .... is relatively enormous in comparison to selective intensities to be expected in nature. (Fertility selection) is sufficient to produce considerable evolutionary changes in relatively short historical periods.
Selection Intensity and Fertility

“Relatively Enormous”

Fisher calculated that selection intensities attributable to heritable differences in fertility could be as high as 95% per generation, based on modest estimates of variance and birth rates in 1930 of 3.9 children per woman, and a standard deviation attributable to heritable fertility of 1.7 children per family.

This compares with maximum estimates of selection advantage attributable to differential mortality in:

- heterozygosity for sickle cell protecting against malaria ~ 10%
- Lactose Intolerance ~10% (genetic and behavioural) (Cavalli Sforza 1998)
- putative resistance to TB ~ 7% (Lipsitch & Sousa 2002)
Undernutrition

Visceral Fat

Hyperandrogenism

Insulin Resistance

Hyperinsulinemia

Chronic Undernutrition

Food Abundance and Sedentism

Normal Ovarian Morphology

Sustained Ovulation

Sustained leptin secretion

Sustained oxidisable fuel

Decreased Glucose uptake by muscle

Fertility First (FF) Genotype

Fertility Selection for FF Genotype

Fertility Selection against FF Genotype

Polycystic Ovaries, PCOS & Ovarian Infertility

Arrested Ovarian Folliculo-genesis

Type 2 Diabetes

Increasing mean BMI

Fertility Selection for FF Genotype

Fertility Selection against FF Genotype

Chronic Undernutrition

Food Abundance and Sedentism
Insulin Resistance and Insulin Sensitivity
Phenotypes held in balance by fertility?

1. The high global prevalence of PCOS, a heritable and common cause of ovarian infertility is an evolutionary paradox

2. This genotype has probably derived from the pre-agrarian past. The transition to agrarianism was associated with poorer nutrition and health. In this circumstance the PCOS genotype persisted because it provided a fertility advantage in chronically undernourished populations.

3. The “escape from hunger” following the agricultural and industrial revolutions was a dramatic change in average conditions for human populations, a change that has now extended to over two thirds of humanity.

4. This change would have reversed the direction of natural but particularly fertility selection for this genotype. Fertility selection is capable of effecting very rapid changes in the prevalence of a gene in a population. This dramatic change in prevalence if it did occur is likely to have coincided with fertility transition.

5. The close association between PCOS, diabetes and the metabolic syndrome suggests a role for this selection event in the evolution of susceptibility to these conditions in human populations.
The Escape From Hunger
Three 18th century French Revolutions

La Liberté guidant le peuple
(Liberty Leading the People)
Eugène Delacroix 1830
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# Evolution of Type 2 Diabetes in Human Populations

*Salience*

<table>
<thead>
<tr>
<th>Category</th>
<th>Topic</th>
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<tbody>
<tr>
<td><strong>Nutritional anthropology</strong></td>
<td>Hunter gatherer</td>
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<td>Diet and nutritional status in agrarian period</td>
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<td></td>
<td>The escape from hunger</td>
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<tr>
<td><strong>Epidemiology</strong></td>
<td>Why is T2D so common and so strongly linked to obesity</td>
</tr>
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<td>A hierarchy of T2D susceptibility, especially relative immunity of Europid populations</td>
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<td>Evolutionary paradox of PCOS, a T2D linked condition</td>
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<td><strong>Pathophysiology of T2Diabetes</strong></td>
<td>Thrifty or Not?</td>
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<td>Does Beta Cell Dysfunction precede IR</td>
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<tr>
<td><strong>T2D Genetics</strong></td>
<td>Recent Evidence of Positive Selection in the Human Genome</td>
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</table>
Evolution of Type 2 Diabetes in Human Populations

4 Hypotheses

1. That over the last 2 million years the metabolic demands of encephalisation drove our hunter gatherer ancestors to develop a metabolic profile more akin to committed carnivores than to other higher apes.

2. That the transition from a predominantly hunter gatherer to agrarian lifestyle had a number of important effects:
   - inverted the ratio of protein:CHO in the diet from 65:35 to 35:65
   - increasing the requirements for insulin: ? Adaptation by increased plasticity β cell function.
   - reduced caloric intake and dietary diversity among agrarians resulted in worse nutrition overall, shorter stature, increase in infectious disease and dental caries

3. This worsening nutrition imposed a fertility constraint on the adaptation to higher levels of carbohydrate intake i.e. those better able to metabolise CHO were less fertile on average.

4. The Escape from Hunger, beginning in Europe in 18th Century, increased average daily caloric intake per capita by about 80 calories per decade, released populations from this fertility constraint, resulting in
   - Initial increase in fertility and population growth
   - a vary rapid increase, through the mechanism of fertility selection, in the prevalence of the adaptive (insulin sensitive) genotype, beginning in European populations
   - This rapid selective event most likely occurred during fertility transition
The Metabolic Demands of Encephalisation

A. afarensis
A. africanus
early Homo
H. erectus
H. sapiens
The Metabolic Demands of Encephalisation

The gut-brain hypothesis

<table>
<thead>
<tr>
<th>Species</th>
<th>Stomach</th>
<th>Small Intestine</th>
<th>Caecum</th>
<th>Colon</th>
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<td>Gorilla</td>
<td>25</td>
<td>14</td>
<td>7</td>
<td>53</td>
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<tr>
<td>Orangutan</td>
<td>17</td>
<td>28</td>
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<td>54</td>
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<tr>
<td>Chimpanzee</td>
<td>20</td>
<td>23</td>
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<td>52</td>
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<tr>
<td>Gibbon</td>
<td>24</td>
<td>29</td>
<td>2</td>
<td>45</td>
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<tr>
<td>Human</td>
<td>17</td>
<td>67</td>
<td>na</td>
<td>17</td>
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*Table 2: Relative gut volume proportions for some primate species (percentage of total volume)*
Low Glucokinase Activity and High Rates of Gluconeogenesis Contribute to Hyperglycemia in Barn Owls (Tyto alba) after a Glucose Challenge¹

Merrick R. Myers and Kirk C. Klasing²

Department of Animal Sciences, University of California, Davis, CA 95616

Plasma Concentration of Glucose in Non Diabetic, Non Insulin Dependent Diabetes and Glucose Intolerant subjects

Adapted from
Dineen et al NEJM327,10 p707
The Carnivore Hypothesis

• Humans consume a diet much higher in quality than is expected for our size and metabolic needs.

• This energy-rich diet appears to reflect an adaptation to the high metabolic cost of our large brain.

• Evidence from the hominid fossil record implies that major changes in diet and relative brain size occurred with the emergence of the genus *Homo*

What is the nature of human adaptation to the agrarian diet?
The Interdependence of $\beta$ cell Function and Insulin Resistance
Linking Insulin Resistance and β cell function

Two Models Proposed: Open and Closed Loops

**Open Loop**

- Environment $\rightarrow$ ↑FFA & cytokines $\rightarrow$ IR & β cell dysfunction
- Genes: mutations in key genes eg IRS-2 calpain-10 affect both IR and β cell dysfunction

**Closed Loop**

- Defective feedback mechanisms ? Glucose. ? Insulin

Bergmann, Finegold, Kahn 2002
The evolution of β-cell dysfunction and insulin resistance in type 2 diabetes

R. N. Bergman, D. T. Finegood and S. E. Kahn
GDM and Plasticity of β cell Function

Fig. 3. Insulin sensitivity-secretion relationships in normal women and women with GDM. The insulin sensitivity index is shown in Fig. 2, right. Prehepatic insulin secretion was assessed during steady-state hyperglycemia using plasma insulin and C-peptide concentrations and C-peptide kinetics in individual patients (21).

Bergman 2002
A Map of Recent Positive Selection in the Human Genome

Benjamin F. Voight, Sridhar Kudaravalli, Xiaoquan Wen, Jonathan K. Pritchard


<table>
<thead>
<tr>
<th>Population</th>
<th>rsnumber</th>
<th>iHS</th>
<th>cM Span</th>
<th>Genes</th>
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<td>-2.842</td>
<td>1.39</td>
<td>GBA, MTX1, ADAM15, LENEPE *</td>
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<td>1.29</td>
<td>NEK1, SH3MD2, CLCN3 *</td>
</tr>
<tr>
<td></td>
<td>rs1442490</td>
<td>-2.665</td>
<td>1.16</td>
<td>ADH cluster, MTP *</td>
</tr>
<tr>
<td>CEPH</td>
<td>rs6035877</td>
<td>-2.194</td>
<td>1.25</td>
<td>XRN2, PAX1, NKX2-2 *</td>
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<tr>
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<td>rs1426721</td>
<td>-2.237</td>
<td>1.15</td>
<td>SLC24A5, SLC12A1, MYEF2, FBN1 *</td>
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<td>rs6497253</td>
<td>-3.118</td>
<td>1.13</td>
<td>OCA2, HERC2</td>
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<tr>
<td>Yoruba</td>
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<td>-2.577</td>
<td>0.97</td>
<td>FBXL7</td>
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<tr>
<td></td>
<td>rs13332060</td>
<td>-2.547</td>
<td>0.94</td>
<td>ATPV0C, CCNF, NTN2L, PDPK1 *</td>
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<tr>
<td></td>
<td>rs9536046</td>
<td>-4.15</td>
<td>0.74</td>
<td>NEK3, ATP7B, CKAP2, LECT1 *</td>
</tr>
</tbody>
</table>

The longest haplotypes around derived alleles ...1.25 cM in Europeans (near NKX2–2, which is involved in insulin regulation). These long haplotypes indicate extremely strong selection on recent mutations, though it is difficult to be confident about the actual genetic target of the selective events.

In summary, the selection events that we detect are generally very recent, substantially postdating the separation times of these populations, and falling mainly within the agricultural phase of human evolution.
Beta Cell plasticity: A Farmers Gene?

The advance of farming in the neolithic period

The distribution of “farmers genes in European populations

Falsifying the Fertility First Hypothesis

Girls with anorexia nervosa who have higher levels of insulin and blood glucose should return to months earlier than those with lower BSL and insulin.

Famine survivors who were able to conceive during the famine would be more likely to develop diabetes in later life. (There are well established famine survivor cohorts in the Netherlands, St Petersburg, Bangladesh and China.)

The international hierarchy of PCOS prevalence should mirror that of Type 2 diabetes.
Some Possible Implications

If sustained this hypothesis has relevance the global epidemic of chronic disease. Does it mean that these epidemics will be tempered by rapid selection against a phenotype which confers a high risk for the development of diabetes.

- Resident and emigrant Japanese populations, already well studied may be able to provide some insight

What are the implications for fertility transition, still to be completed in many of the world’s poorest populations