Impact on benefit testing, while targeting specific groups

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Major causes of mortality and morbidity

- Cardiovascular disease
  - Coronary Heart Disease
  - Stroke

- Cancer

- Type 2 diabetes and its complications

- Dementia
Chronic Disease Risk

• Diet and lifestyle (physical activity, smoking, alcohol intake) are major determinants of risk

• Genome wide association studies have failed to find major determinants of the major chronic diseases

• The size of diet x genetics interactions are uncertain

• Increasing age is the biggest risk factor for non-communicable diseases

• Many disease processes are self-amplifying and develop over long periods of time that are not amenable to short term interventions
At risk groups

- Older adults
- Groups with strong family history of the disorder
- Individuals with a genetic susceptibility
Ethnic diversity

• Different dietary habits

• Different risk profiles vs. White Europeans
  – black Africans more likely to be hypertensive and are greater risk of stroke
  – South Asians more likely to have atherogenic dyslipidemia (raised TAG, low HDL)
Figure 1 Numbers of people with diabetes (in millions) for 2000 and 2010 (top and middle values, respectively), and the percentage increase. Data adapted from ref. 2.
Types of evidence

Direct relationship

Potential for confounding

Heart attacks

Indirect effect

Risk factors (may be altered in different directions)

Other factors
Hierarchy in Scientific Evidence

- Systematic Reviews (Meta-analysis)
- Randomized Controlled Trials
- Other Controlled Trials
- Prospective Cohort studies
- Case – Control studies
- Prevalence studies
- Ecological studies
- Animal studies
Food health benefit claims

• Usually based on a hypothetical effect on the disease process via an effect on a surrogate marker rather than evidence of disease reduction

• Data from prospective epidemiological studies indicate association rather than causality and can be confounded

• Demonstrating benefit in terms of chronic disease reduction is difficult
The relationship between body mass index (BMI) and mortality rate is J-shaped (data excludes those who died within 5 years).

Mortality rates from different causes by body mass index (BMI)

Note the differences in scale and women are fatter than men

Limitations of the use of surrogate risk markers for disease

• Diet may influence risk markers is different directions making interpretation difficult
  – e.g. Saturated fatty acids increase LDL cholesterol (harmful) but also increase HDL cholesterol (beneficial)

• Besides insulin sensitivity, blood pressure and total cholesterol/HDL cholesterol few other surrogate risk markers are accepted as robust indices of risk
Limitations of genome wide associations

- Large cross sectional studies “looking for a needle in a haystack”
- Statistically limited by multiple comparisons which means true differences may be overlooked by setting the level of probability too high
- Inability to assess gene x environment interactions
Diet x genetic interactions

• Most studies have been post-hoc analyses rather than prospective. The size of the effects is small

• Many scientific journals are requiring evidence of replication of findings before publication
ApoE gene polymorphisms

- 2 SNPs in exon 4 result in 3 alleles (E2, E3, E4)
  - 3 homozygous (E2/E2; E3/E3; E4/E4)
  - 3 heterozygous (E2/E3; E2/E4; E3/E4)
- Allele frequencies in population
  
  \[
  \begin{align*}
  E2 & \sim 8\% \\
  E3 & > 60\% \\
  E4 & \sim 15\%
  \end{align*}
  \]
ApoE polymorphisms: effect on cholesterol levels

• Alter levels of total and LDL cholesterol
• Account for ~ 8-10% of total plasma and LDL cholesterol variation in population
  – E3: ‘normal’ benchmark
  – E2: lower plasma total and LDL cholesterol but high TAG
  – E4: higher plasma total and LDL cholesterol
ApoE phenotype

<table>
<thead>
<tr>
<th>ApoE phenotype</th>
<th>LDL cholesterol mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2:E2 0.9%</td>
<td></td>
</tr>
<tr>
<td>E2:E3 12.9%</td>
<td></td>
</tr>
<tr>
<td>E3:E3 62.9%</td>
<td></td>
</tr>
<tr>
<td>E2:E4 1.9%</td>
<td></td>
</tr>
<tr>
<td>E3:E4 18.3%</td>
<td></td>
</tr>
<tr>
<td>E4:E4 3.0%</td>
<td></td>
</tr>
</tbody>
</table>
### ApoE genotypes and risk of CHD

#### Table 2. Pooled Odds Ratios for Risk for Coronary Heart Disease, according to Apolipoprotein E Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Overall Frequency (Range), %*</th>
<th>Studies (Case-Patients/Controls), n (n/n)</th>
<th>Pooled Estimates of Odds Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>e3/3</td>
<td>61.0 (21.7–81.9)</td>
<td>41 (8723/17 064)</td>
<td>Random-Effects Model (95% CI)†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>e2/2</td>
<td>0.71 (0.27–4.63)</td>
<td>27 (105/178)</td>
<td>1.19 (0.92–1.54)</td>
</tr>
<tr>
<td>e2/3</td>
<td>11.4 (2.63–17.5)</td>
<td>41 (1362/3181)</td>
<td>0.95 (0.84–1.07)</td>
</tr>
<tr>
<td>e2/4</td>
<td>2.32 (0.64–7.23)</td>
<td>39 (284/645)</td>
<td>0.98 (0.84–1.14)</td>
</tr>
<tr>
<td>e3/4</td>
<td>22.6 (7.89–52.2)</td>
<td>41 (3532/6319)</td>
<td>1.30 (1.18–1.44)</td>
</tr>
<tr>
<td>e4/4</td>
<td>2.22 (0.24–5.56)</td>
<td>38 (360/606)</td>
<td>1.35 (1.17–1.56)</td>
</tr>
</tbody>
</table>

* Based on the available data among controls of included studies for each genotype.
† DerSimonian and Laird random-effects model (without controlling for study-level covariates).
‡ Adjustment for study-level variables, including the mean age of case-patients, sex, continent of origin, study design, the use of controls, genotype frequency among controls, the presence or absence of the Hardy–Weinberg equilibrium among controls, and genotyping methods.

Song et al *Ann Intern Med* 2004;141:137-147
E2 & E4 alleles confer different binding affinity to LDL receptors in liver

**E4:** high receptor binding ability

- competitive binding to LDL receptor in liver
- reduced LDL uptake and accumulation in circulation
- pro-atherogenic

**E2:** defective receptor binding affinity

- slow to clear chylomicrons & VLDL from circulation resulting in high TAG (E2/E2 associated with type III hyperlipidaemia)
- LDL uptake not affected
ApoE genotype and response to low and high cholesterol diets

High cholesterol diet

- Subjects followed reduced cholesterol diet, then same diet with additional cholesterol
- ApoE4 homozygotes showed greatest decrease in serum lipid with low cholesterol, and greatest increase in serum lipid with additional cholesterol

ApoE 4/4 genotype is highly responsive to modifications of dietary cholesterol

ApoE genotype interaction with diet

• High LDL cholesterol in E4 carriers manifests only in populations consuming diets high in fat and cholesterol

• ~ 46 intervention studies involving altering fat/cholesterol content of diet

• Consensus is that E4 carriers greatest response to increased or decreased dietary cholesterol intake and thus are most likely to benefit from restricting cholesterol intake
Epigenetic effects

• Diet may have its influence on adult disease risk by “programming” in early life

• e.g. Low birth weight followed by accelerated growth in infancy increases risk of developing metabolic syndrome and hypertension in adult life
Benefits of targeting at risk groups

- Heavy drinkers – benefits obvious
- Overweight/obese – depends on absolute risk
Dangers of targeting at “risk groups”

• Public health measures are aimed at the whole population not individuals
• Most disease occurs as random events
• Products that target at risk individuals may encourage risk taking behaviour
• At risk individuals may prefer to follow an unproven dietary regimen rather than taken proven medication
Defining benefit

• Appropriate target group

• Appropriate choice of primary outcome
  – Clinical events
  – Disease progression
  – Surrogate marker of risk

• Is the “dose” of food in the normal physiological range

• Sufficient duration of the study

• Evidence of compliance to protocol

• Sufficient statistical power

• Trials need to conform to CONSORT guideline
Problem definition

- The status quo is that diets are currently high in SFA the alternative situation is to partial replace them with MUFA

- The question is thus what are the benefits of replacing SFA with MUFA
Blood lipid metrics of risk of CHD

Prospective Studies Collaboration. Lancet 2007;9602:1829-1839
FIGURE 1. Predicted changes (Δ) in the ratio of serum total to HDL cholesterol and in LDL- and HDL-cholesterol concentrations when carbohydrates constituting 1% of energy are replaced isoenergetically with saturated, cis monounsaturated, cis polyunsaturated, or trans monounsaturated fatty acids.

Coronary Heart Disease

High LDL-C

Metabolic Syndrome

Type 2 Diabetes
Subcutaneous Adipose Tissue

Weight loss ~ 10%
Loss of visceral AT ~ 30%

- Diet
- Exercise
- Pharmacotherapy

<table>
<thead>
<tr>
<th>Deterioration</th>
<th>Lipid profile</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired</td>
<td>Insulin sensitivity</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>Blood Insulin</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>Blood Glucose</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>Risk markers</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>For thrombosis</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>Inflammatory Markers</td>
<td>Improved</td>
</tr>
</tbody>
</table>

- Increased CV risk
- Low

Abdominal obesity
Increased waist circumference

After weight loss
Reduced waist circumference

IMPACT OF THE AMOUNT AND TYPE OF FAT AND CARBOHYDRATE ON METABOLIC SYNDROME AND CARDIOVASCULAR DISEASE RISK
Control diet: ‘average UK diet’ = high SFA/high GI

Study design: 5 Diets

- High MUFA
- High GI
- Lower fat
- Low GI
1 month run-in

Six-month dietary intervention using every-day foodstuffs in subjects with metabolic syndrome

Run-in on Control diet (18% SFA; 38% fat; High GI)
Randomized to either
1. Control
2. MUFA Hi-Gl (10% SFA, 38% fat)
3. MUFA Lo-Gl (10% SFA, 38% fat)
4. Low fat Hi-Gl (10% SFA, 28% fat)
5. Low fat Lo-Gl (10% SFA, 28% fat)
Entry criteria

Target groups (all 5 centres)

- Family history of type II diabetes
- Gestational diabetes
- Polycystic ovary syndrome
- Asians
- Atherogenic lipoprotein phenotype (TAG > 1.5 mmol/l, HDL-C < 1.3 mmol/l)
- Impaired fasting plasma glucose (6.1 - 6.9 mmol/l)

Screening criteria

- Insulin resistance
  - Fasting glucose > 5.5 mmol/l (3)
  - OR
  - Fasting insulin > 40 pmol/l (3)

- Dyslipidaemia
  - HDL-C < 1.0 mmol/l (2)
  - TAG > 1.3 mmol/l (1)

- Hypertension
  - ≥ 140 mmHg (1) / ≥ 90 mmHg (1)
  - (Treated or untreated)

- Central adiposity
  - Waist circumference
    - > 94 cm (1)
    - > 102 cm (2)
  - OR
  - Obesity
    - BMI 25-30 (1)
    - > 30 (2)

Score ≥ 4 to enter study (max = 10)
CONSORT (CONsolidated Standards of Reporting Trials) diagram of subject flow throughout the trial.

Assessed for eligibility  
(n = 1536)

Nonattendance n = 220  
Not meeting inclusion criteria  
(n = 458)  
Withdrawn (n = 138)

Randomized  
n = 720

HS/HGI  
(n = 137)  
Lost to follow-up  
(discontinued)  
(n = 52)  
Completed  
(n = 85)

HM/HGI  
(n = 145)  
Lost to follow-up  
(discontinued)  
(n = 34)  
Completed  
(n = 111)

HM/LGI  
(n = 144)  
Lost to follow-up  
(discontinued)  
(n = 28)  
Completed  
(n = 116)

LF/HGI  
(n = 145)  
Lost to follow-up  
(discontinued)  
(n = 29)  
Completed  
(n = 116)

LF/LGI  
(n = 149)  
Lost to follow-up  
(discontinued)  
(n = 28)  
Completed  
(n = 121)

Change in insulin sensitivity Si on diet

% change in Si with 95% CI

P = 0.13 from ANCOVA adjusted for gender, centre, ethnicity, age and baseline waist measurement and change in weight
Mean (±SEM) changes in cholesterol, apolipoprotein B (ApoB), and apolipoprotein A1 (ApoA1) after consumption of diets low in saturated fatty acids (SFA) that were high in monounsaturated fatty acids or low in fat compared with a control saturated fat–rich diet.

No differences between SFA and MUFA

• Blood pressure
• Small dense LDL
• Markers of inflammation - C-reactive protein
• Fibrinogen
• Factor VII
• Fibrinolytic activity (PAI-1)
• Arterial stiffness
• Endothelial function
Risk ratios and 95% CIs for fully adjusted random-effects models examining associations between saturated fat intake in relation to coronary heart disease and stroke.

Effect on risk of CHD events of replacing 5% energy saturated fatty acids from pooled analysis of 11 cohort studies

Conclusion of risk benefit analysis of replacing SFA with MUFA

• There is no clear evidence of benefit from replacing SFA with MUFA on CHD risk
Conclusion – benefit testing

- The target group should be defined on entry to trial
- The research question needs to be clearly formulated with one primary outcome
- The number of secondary outcomes should be limited because of the penalties of multiple testing
- Studies need to be appropriately powered and evidence of compliance to treatment protocol provided