Intermittent Fasting
What is the Evidence?

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Genesis Prevention Centre
University Hospital of South Manchester

BNF Half-day Symposium: Popular Diets - What is the evidence?
January 8th 2014
The History of Intermittent Fasting

Animal studies

• 1909  Energy restriction prevents cancer
• 1946  Intermittent energy restriction prevents cancer
• 2000  Intermittent equivalent or superior to daily restriction to reduce breast, prostate, pancreatic tumours, sarcoma, lymphoma, CVD & dementia

Variety of regimens studied

• Alternate day fasting
• 3 weeks 50% restriction & 3 weeks ad lib
• Alternate weeks of 50% restriction & ad lib

Intermittent restriction includes spells of more severe restriction which could mobilise visceral fat, reduce oxidative stress & cell proliferation
Two main rationales for intermittent energy restriction

1. May be easier to follow than daily diets?

2. May have better metabolic effects?
Human studies

Normal weight

2005 Alternate day fasting 3 weeks \((n = 16)\)

Weight loss research

2 Day Diet
Harvie M et al 2010
Harvie M et al 2013

Alternate Day Fasting
Johnson JB 2007
Varady K et al 2009

Eat, Fast and Live longer (Horizon Mosley) Aug 2012

Harvie M et al Int J Obes 35:714-727, 2010
Harvie M et al Br J Nutr 2013
Energy restriction is difficult to achieve & maintain in humans!

25-30% adherence to low cal diets at 12 months

20-40% achieve > 5% weight loss at 1 year

Only 20% of women at high risk of breast cancer maintain > 5% weight loss at 5 years with daily restricted diets.

Some metabolic benefits of weight loss attenuate once dieters reach a stable weight & are no longer in energy deficit.

Wadden et al *Obes Res* 7 170 – 178
Study 1 – RCT of intermittent vs. daily energy restriction 2006-2009

1. Is intermittent energy restriction (IER) acceptable & easier to follow than daily restriction?

2. Does IER have better effects on risk markers for breast cancer, diabetes, CVD compared to daily restriction?
Intermittent energy restriction

Our 5:2 diet

Overall 25% energy restriction

Daily energy restriction: 25% restriction 7 days/week

Intermittent energy restriction 75% restriction 2 days/week
Study 1

**Intermittent (n = 52)**
- 2 days ~650 kcal:
  - 2 pints semi-skimmed milk
  - 1 fruit & 4 vegetable
  - 2 pints low-calorie drinks
- 5 days ~1900 kcal/day
  - Mediterranean diet

**Daily (n = 52)**
- 7 days
  - ~1500 kcal/day
  - Mediterranean diet

6 months
- Weight, body fat and waist
- Markers of disease risk: Insulin, leptin, adiponectin, testosterone, growth factors (IGF-1), inflammation, oxidative stress
Study 1 – main findings

Intermittent dieters lost 6kg fat  Daily dieters lost 4.9kg fat (numerically but not statistically greater)

Intermittent diet has beneficial effects on metabolism during & after restricted days:

Better at reducing insulin on “non diet” days (-30 vs. -17% reduction)
Additional 25% reduction in insulin on diet days

Simple “milk and veg” intermittent diet was not much easier to follow than a daily diet

Study 2 Trial of Intermittent vs. Daily Energy Restriction

Overweight women randomised to three groups
N = 115

3 months weight loss

- 25% restriction
  - 2 day low CHO low energy
  - 5 days Med diet

1 month weight loss maintenance

- 1 day low carbohydrate low energy

- Maintenance Med diet

- 2 day ad lib low carbohydrate
  - 5 days Med diet

- 1 day ad lib low carbohydrate
Study 2 - Diets

**Intermittent low carbohydrate**
- Low energy
- 2 days / week (~650 kcal)
- <50g carbohydrate
- ~10oz of protein foods
- Limited dairy foods
- 5 veg & 1 fruit
- 5 days / week
- Ad lib
- Mediterranean diet

**25% restricted Mediterranean diet**
- 7 days / week
- ~1500 kcal / day
- Mediterranean diet
- 30% fat:
  - 15% MUFA, 7% PUFA
  - 7% saturated fat
  - 45% low GI carbohydrate
  - 25% protein

**Intermittent low carbohydrate**
- Ad Lib
- 2 days / week (~1000 kcal)
- <50g carbohydrate
- Unlimited meat, fish, eggs, tofu, MUFA and PUFA fats,
- Limited dairy foods,
- 5 veg & 1 fruit
- 5 days / week
- Ad lib
- Mediterranean diet
Study 2 - Change in weight & body fat including drop outs (N = 115)


Drop outs
Intermittent = 4
Intermittent low carb = 10
Daily = 13
## Study 2 - Weight & insulin at 3 months (N = 115)

<table>
<thead>
<tr>
<th></th>
<th>Restricted 2 DAY (n=37)</th>
<th>AD LIB 2 DAY (n= 38)</th>
<th>Daily energy restricted diet (n=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losing &gt; 5% weight</td>
<td>65%</td>
<td>60%</td>
<td>37%</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Waist reduction (cm)</td>
<td>-5.2 (-7.1 to -3.9)</td>
<td>-4.7 (-6.0 to -3.4)</td>
<td>-3.7 (-4.7 to -1.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Insulin % change</td>
<td>-22 (-35 to -11)%</td>
<td>-14 (-27 to -5%)</td>
<td>-4 (-16 to 9)%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Mean (95% confidence interval)*

## Study 2 - adherence

<table>
<thead>
<tr>
<th></th>
<th>Restricted 2 DAY (n=37)</th>
<th>AD LIB 2 DAY (n=38)</th>
<th>Daily energy restricted diet (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adherence to prescribed diet</strong></td>
<td>76% of potential 2 days</td>
<td>74% of potential 2 days</td>
<td>39% of days when achieve target 25% restriction</td>
</tr>
<tr>
<td><strong>Intake on non diet days</strong></td>
<td>1360 (1241 to 1400)</td>
<td>1533 (1400 to 1667)</td>
<td>1459 (1327 to 1590)</td>
</tr>
</tbody>
</table>

*Mean (95% confidence interval)*

Study 2 - day ad lib v continuous

<table>
<thead>
<tr>
<th>Energy restriction %</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

2 Day Diet

- Insulin: -27%
- Ketones: +78%

Continuous

Week 1

Week 2 etc
Intermittent diet study 2- Summary

1. IER superior to daily restriction for reducing body fat & insulin.
2. 2 day ad lib low carb is equivalent to 2 days energy restricted diet
3. 1 day of restriction / week maintains weight loss
**Alternate day fasting**

3 – 4 “Fast days” per week
25% energy requirement i.e. 400- 600 kcal

3 – 4 “feast days” per week
Ad lib low fat / American Heart Association diet

<table>
<thead>
<tr>
<th>Example Fast day</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lunch</strong></td>
<td>Chicken fettucini</td>
<td><strong>Energy</strong> 450 Kcal</td>
</tr>
<tr>
<td><strong>Fruit/ veg</strong></td>
<td>Apple</td>
<td><strong>Fat</strong> 13 g</td>
</tr>
<tr>
<td><strong>Snack</strong></td>
<td>Cookie</td>
<td><strong>Protein</strong> 25g</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Carbohydrate</strong> 60g</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Fibre</strong> 10g</td>
</tr>
</tbody>
</table>
## Alternate day fasting trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Weeks</th>
<th>Dropout</th>
<th>Weight loss -%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson 2007</td>
<td>10 ADF</td>
<td>8</td>
<td>1</td>
<td>-8 (1.5)</td>
</tr>
<tr>
<td>Varady 2009</td>
<td>20 ADF</td>
<td>8</td>
<td>4</td>
<td>-4 (1.1)</td>
</tr>
<tr>
<td>Varady 2011</td>
<td>15 ADF</td>
<td>12</td>
<td>11/60</td>
<td>-5.2(1.1)</td>
</tr>
<tr>
<td></td>
<td>15 CER</td>
<td></td>
<td></td>
<td>-5.0(1.4)</td>
</tr>
<tr>
<td></td>
<td>15 EX</td>
<td></td>
<td></td>
<td>-5.1(0.9)</td>
</tr>
<tr>
<td></td>
<td>15 control</td>
<td></td>
<td></td>
<td>-0.2(0.4)</td>
</tr>
<tr>
<td>Klempel 2013</td>
<td>18 high fat ADF</td>
<td>8</td>
<td>15/18</td>
<td>-4.8(1.0)</td>
</tr>
<tr>
<td></td>
<td>18 low fat ADF</td>
<td></td>
<td>17/18</td>
<td>-4.2(0.8)</td>
</tr>
<tr>
<td>Bhutani 2013</td>
<td>25 ADF</td>
<td>12</td>
<td>9</td>
<td>-3.0(1)**</td>
</tr>
<tr>
<td></td>
<td>18ADF+EX</td>
<td></td>
<td>2</td>
<td>-6.5(4)</td>
</tr>
<tr>
<td></td>
<td>24EX</td>
<td></td>
<td>8</td>
<td>-1.0(0)</td>
</tr>
<tr>
<td></td>
<td>16 Control</td>
<td></td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Eshghinia 2013</td>
<td>15</td>
<td>6</td>
<td>?</td>
<td>-7.1(3)</td>
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*mean (SEM)  Weight after ad lib day  **ITT analysis
## Alternate day fasting trials

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<td>8</td>
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<td>12</td>
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* mean (SEM)  
Weight after ad lib day  
**ITT analysis
# Intermittent diet summary

<table>
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<tr>
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<th>2 day diet</th>
<th>Alternate day fast</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total patients studied</strong></td>
<td>129</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>+73 in on going trials</td>
<td>+ 25 unpublished</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>129 female</td>
<td>100 female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 Male</td>
</tr>
<tr>
<td><strong>Recruitment</strong></td>
<td>Family history clinic</td>
<td>Answered advert</td>
</tr>
<tr>
<td><strong>Support</strong></td>
<td>Self selected food Monthly face to face &amp; biweekly phone review dietitian</td>
<td>Diet days meals provided Weekly review with dietitian</td>
</tr>
<tr>
<td><strong>RCT vs. daily diet</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Intake on unrestricted days</strong></td>
<td>-25%</td>
<td>+ 15%</td>
</tr>
<tr>
<td><strong>Overall energy restriction</strong></td>
<td>30 – 36%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Duration of studies</strong></td>
<td>4 &amp; 6 months</td>
<td>2-3 months</td>
</tr>
<tr>
<td><strong>Maintenance regimen</strong></td>
<td>1 day</td>
<td>Not studied</td>
</tr>
</tbody>
</table>
First 5:2 book published Oct 2012
Jan 5th 2014 ~130 books & increasing!
Myths about 5:2 diets

1. 5:2 diets: 500-600 kcal for 2/days/week & eat what you want 5 days/week have not been researched!

1. You can eat what you want on non-diet days and still lose weight and protect yourself against disease.

2. You can just focus on calories and it does not matter what types of foods we eat.

3. Intermittent diets are proven to have health benefits if you are a healthy weight.

5. You need to take nutritional supplements.
Intermittent diets are a potential alternative to daily diets.

No evidence that intermittent leads to disordered eating or unhealthy diets.

Appear to have beneficial effects on metabolism i.e. insulin resistance.
What we need to know

More data on the long term success & safety of IER

?Rolled out in clinical practice?

2 days/week or ADF work but what is the ideal IER for health? How low in calories? How long? & How often?

Application in other populations i.e. diabetes, morbid obesity

Do intermittent diets target loss of fat and preserve muscle mass & maintain REE?

Are there any benefits of IER in healthy weight people? i.e. can one day week of IER prevent weight gain & disease
## Acknowledgements

### The Patients

<table>
<thead>
<tr>
<th>FAMILY HISTORY CLINIC</th>
<th>LIFESTYLE</th>
<th>COLLABORATORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tony Howell</td>
<td>Mary Pegington</td>
<td>Rob Clarke – Patterson Institute</td>
</tr>
<tr>
<td>Gareth Evans</td>
<td>Debbie McMullen</td>
<td>Kath Spence – Patterson Institute</td>
</tr>
<tr>
<td>Paula Stavrinos</td>
<td>Kath Sellers</td>
<td>Andy Sims – Breakthrough Edinburgh</td>
</tr>
<tr>
<td>Louise Donnelly</td>
<td>Ellen Mitchell</td>
<td>Roy Goodacre – UOM</td>
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<tr>
<td>R Greenhalgh</td>
<td>Clare Wright</td>
<td>Mark Mattson – NIH Baltimore</td>
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<tr>
<td>Jenny Affen</td>
<td>Pam Coates</td>
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<tr>
<td>Jayne Beesley</td>
<td>Genesis Volunteers</td>
<td></td>
</tr>
</tbody>
</table>

### Funding

- Genesis Breast Cancer Prevention
- National Institute of Health Research
- Breast Cancer Campaign
- WCRF
- Breast Cancer Research Trust
Intermittent energy restriction
Our 5:2 diet

Days
0 2 4 6 8 10 12 14

Energy restriction
-100%
-75%
-50%
-25%
0%
Energy intake with our 5:2 diet

Daily energy restriction: 25% ER 7 days / week

Intermittent energy restriction: 50 - 60% ER 2 days week & 23% ER 5 days / week

The ideal weight loss diet

- Reduces calorie intake
- Acceptable/ palatable/ high satiety
- Promotes fat loss & preserves muscle & REE
- Nutritional adequacy
- Good “motivating” rate of weight loss
- Specific benefits on disease risk factors i.e. insulin sensitivity, lipids.
- Easy to advise
- Promotes weight loss maintenance
Human studies

Normal weight

2005 Alternate day fasting  3 weeks  (n = 16)
(Heilbronn L et al  Am J Clin Nutr 2005)

Weight loss research

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