Combining UK Biobank genetics and MRI imaging data to identify genetic factors associated with higher body fat % but lower risk of diabetes.

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Some people develop diabetes at lower BMIs and some people are healthy at higher BMIs which is partly genetically defined.
Some people develop diabetes at lower BMIs and some people are healthy at higher BMIs which is partly genetically defined.
Genetic factors associated with “favourable adiposity” will help understand mechanisms that delay or protect individuals from type 2 diabetes.

**“Unfavourable adiposity”**

<table>
<thead>
<tr>
<th>Body fat %</th>
<th>Type 2 diabetes Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>31.4</td>
<td>1.11</td>
</tr>
<tr>
<td>31.6</td>
<td>1.22</td>
</tr>
<tr>
<td>31.8</td>
<td>1.35</td>
</tr>
<tr>
<td>32.0</td>
<td>1.50</td>
</tr>
<tr>
<td>32.2</td>
<td>1.65</td>
</tr>
</tbody>
</table>

**“Favourable adiposity”**

<table>
<thead>
<tr>
<th>Body fat %</th>
<th>Type 2 diabetes Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>31.4</td>
<td>0.90</td>
</tr>
<tr>
<td>31.6</td>
<td>0.82</td>
</tr>
<tr>
<td>31.8</td>
<td>0.67</td>
</tr>
<tr>
<td>32.0</td>
<td>0.55</td>
</tr>
<tr>
<td>32.2</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Data from [biobank.uk](https://www.biobank.ac.uk)
We characterized 14 genetic variants associated with “favourable adiposity”.

Body fat % (n = 500,000) UK Biobank

Published genome-wide association analysis

Body fat % (n= 70,000) Lu et al. *Nature communications* (2016).

Triglycerides  (N= 99,900)  UK Biobank

Adiponectin (N= 70,000)  UK Biobank

HDL-C  (N= 99,900)  UK Biobank

Published genome-wide association analysis

Body fat % (n= 70,000)  Lu et al. *Nature communications* (2016).

Associated with **higher** body fat % but **better** metabolic profile

Associated with **higher** body fat % and **adverse** metabolic profile
“Favourable adiposity” variants together were associated with higher adiposity but lower risk of type 2 diabetes, heart disease and hypertension.

<table>
<thead>
<tr>
<th></th>
<th>Body fat %</th>
<th>Type 2 diabetes (Odds ratio)</th>
<th>Heart disease (Odds ratio)</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Diastolic blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 443,000</td>
<td>14,371 cases, 428,017 controls</td>
<td>37,741 cases, 318,892 controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effects Per 5+ alleles</td>
<td></td>
<td>6x10^{-03}</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Data from biobank.uk
The “favourable adiposity” effect is not driven by altered body shape in men detectable by waist-to-hip ratio.

Women: 207,126

Women:
- Waist circumference
- Hip circumference

Men: 175,776

Men:
- Waist circumference
- Hip circumference

Data from biobankuk
We investigated the associations between the “favourable adiposity” variants and MRI/CT scan measures of abdominal adipose tissue.

Visceral and subcutaneous fat (N = 27,766)  
Liver fat (N = 9,210)

- UK Biobank (N = 5,045)
- The Netherlands Epidemiology of Obesity Study (NEO) (N = 2,236)
- Tübingen Family Study for Type-2 Diabetes (TÜF) (N = 833)
- DIRECT (N = 1,320)
- Published GWAS* (N = 18,332)

- UK Biobank (N = 5,045)
- The Netherlands Epidemiology of Obesity Study (NEO) (N = 1,821)
- Tübingen Family Study for Type-2 Diabetes (TÜF) (N = 911)
- DIRECT (N = 1,433)

“Favourable adiposity” variants together were associated with higher subcutaneous fat but lower liver fat.
“Favourable adiposity” alleles have similar effects in South Asians comparing to Europeans, but are less frequent in South Asians.

<table>
<thead>
<tr>
<th>Body fat %</th>
<th>BMI (kg/m²)</th>
<th>Type 2 diabetes (Odds ratio)</th>
<th>Heart disease (Odds ratio)</th>
</tr>
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<td></td>
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</table>

- Average number of alleles: 10.5 vs 11.6; P<0.0001

Data from 451,000 Europeans

10,203 South Asians

Genetic score of “favourable adiposity”
The identification of “favourable adiposity” alleles locate genes that may be targets for novel insulin-sensitizing agents.

Thiazolidinediones (PPAR-γ agonists) redistributes fat away from liver towards an expanded subcutaneous depot.
Acknowledgements

The Genetics of Complex Traits team at Exeter:

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Marcus Tuke
Jessica Tyrrell
Mike Weedon
Andy Wood

Analysis of MRI image data of abdominal & liver fat:

UK Biobank: Jimmy Bell, Alex Blakemore and Andrianos Yiorkas

DIRECT study: Francesca Frau, Louise Thomas, Karla V. Allebrandt, Ewan Pearson

NEO study: Dennis Mook-Kanamori, Renée de Mutsert,

TÜF study: Norbert Stefan, Harald Staiger
The identification of “favourable adiposity” alleles locate genes that may be targets for novel insulin-sensitizing agents.

Thiazolidinediones (PPAR-γ agonists) redistributes fat away from liver towards an expanded subcutaneous depot.

*TRIB1* adipose tissue mass and lipolysis.
*VEGF-A* maintains healthy expansion of adipose tissue and protects from lipotoxicity.
*CITED2* is required for optimal PPARγ activation.
*FAM13A* is in the insulin signaling cascade.
*IRS1*, *CCDC92* and *DNAH10* are associated with adipogenesis, lipid accumulation and adipocyte differentiation.
*KLF14* is a master regulator of gene expression in adipose tissue and associated with adipocyte cell size.
*MAP3K1* regulates expression of IRS1.
*LYPLAL1* maintains triglycerides metabolism.