Loss of function variant in SMIM1 is associated with reduced energy expenditure and weight gain

Luca Stefanucci¹²³⁴*, Camous Moslemi⁴*, Ana R. Tome¹²⁷*, Samuel Virtue⁵, Nicholas S. Gleadall¹², Laura P.E. Watson⁶, Jing Eugene Kwa⁷, Frances Burden¹², Samantha Farrow¹², DBDS Genetic consortium¹, Ji Chen⁸, MAGIC⁵, Uermo Vösa⁹, Keith Burling¹⁰, Lindsay Walker¹², John Ord¹², Peter Baker¹⁰, James Warner⁶, Amy Frary¹¹, Karola Renhstrom¹¹, Sofie E. Ashford¹¹, Jo Piper⁶, Gail Biggs⁶, Wendy N. Erber¹², Gary J. Hoffman¹³, Nadia Schoenmakers⁵, Christian Erikstrup¹⁴, Klaus Rieneck¹⁵, Morten Dziegiel¹⁶, Henrik Ullum¹⁸, Vian Azzu⁵,¹⁹, Michele Vacca⁵,²⁰, Omer A. Bayraktar⁷, Antonio Vidal-Puig⁵,²¹, Sisse R. Ostrowski¹⁶,²², William J. Astle¹²³,²³, Martin L. Olsson²⁴,²⁵, Jill R. Story⁴,²⁵, Ole B. Pedersen²⁶, Willem H. Ouwehand¹²,²⁷, Krishna Chatterjee⁵, Dragana Vuckovic²⁸, Mattia Frontini¹²³⁸,¶

¹ Department of Haematology, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK. ² National Health Service (NHS) Blood and Transplant, Cambridge Biomedical Campus, Cambridge, UK. ³ British Heart Foundation, Cambridge Centre for Research Excellence, University of Cambridge, Cambridge Biomedical Campus, Cambridge, United Kingdom. ⁴ Department of Clinical Immunology, Zealand University Hospital, Køge, Roskilde University, Denmark. ⁵ Wellcome-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, UK. ⁶ NIHR Cambridge Clinical Research Facility, Cambridge University Hospitals, Cambridge Biomedical Campus, Cambridge, United Kingdom. ⁷ Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge, UK. ⁸ Estonian Genome Centre, Institute of Genomics, University of Tartu, Tartu, Estonia. ⁹ NIHR Cambridge Biomedical Research Centre Core Biochemical Assay Laboratory, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. ¹⁰ University of Western Australia, Perth, WA, Australia. ¹¹ Discipline of Pathology and Laboratory Medicine, Medical School, The University of Western Australia, Perth, WA, Australia. ¹² Department of Clinical Immunology, Aarhus University Hospital, Aarhus University, Denmark. ¹³ Department of Clinical Immunology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. ¹⁴ Department of Gastroenterology, Norfolk & Norwich University Hospitals NHS Foundation Trust, Norwich, UK. ¹⁵ Disciplín of Pathology and Laboratory Medicine, Medical School, The University of Western Australia, Perth, WA, Australia. ¹⁶ Blood Bank KI 2034, Department of Clinical Immunology, Copenhagen University Hospital, Copenhagen, Denmark. ¹⁷ Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. ¹⁸ Statens Serum Institut, Copenhagen, Denmark. ¹⁹ Department of Gastroenterology, Norfolk & Norwich University Hospitals NHS Foundation Trust, Norwich, UK. ²⁰ Interdisciplinary
Stefanucci et al

Department of Medicine, Università degli Studi di Bari “Aldo Moro”, Bari, Italy. 
Institute of Metabolic Science and Medical Research Council Metabolic Diseases Unit, University of Cambridge, Cambridge, UK. 
Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. 
MRC Biostatistics Unit, East Forvie Building, Cambridge Biomedical Campus, University of Cambridge, Cambridge, UK. 
Clinical Immunology and Transfusion Medicine, Office for Medical Services, Lund, Region Skåne, Sweden. 
Department of Laboratory Medicine, Division of Hematology and Transfusion Medicine, Lund University, Sweden. 
Department of Clinical Immunology, Zealand University Hospital, Køge, University of Copenhagen, Denmark. 
Department of Haematology, University College London Hospitals NHS Trust, London. 
Department of Laboratory Medicine, Division of Hematology and Transfusion Medicine, Lund University, Sweden. 

*These authors contributed equally

†Correspondence to MF: m.frontini@exeter.ac.uk or mf471@cam.ac.uk

¶Full list of consortium members in the supplementary text

Abstract

Blood group antigens are the archetypal example of human genetic variation. Here, we characterised the functional metabolic consequences in individuals homozygous for a 17bp deletion in \textit{SMIM1} (rs566629828; minor allele frequency 0.0147) and thus lacking the protein defining the Vel blood group. Our analysis, in separate cohorts of \textit{SMIM1}-/- individuals (UK Biobank, NHS Blood and Transplant, Danish Blood Donor Study, Copenhagen Hospital Biobank) and a mouse model, identified an increase in body weight accompanied by a range of metabolic differences, including dyslipidemia, changes in the leptin-adiponectin ratio, increased liver enzymes and lower total thyroid hormone levels. These changes in the metabolic state were at least in part due to a reduction in resting energy expenditure, as assessed during an in-depth clinical assessment of \textit{SMIM1}-/- individuals. Additionally, electronic health records suggest that individuals lacking this 78-amino-acid type II transmembrane protein may be more prone to cerebral bleeds and thrombotic stroke.

Main text

Over 1500 variants in 48 genes underlie the range of antigens categorised into 43 blood group systems. Common loss-of-function (LoF) variants in the \textit{ABO} and \textit{RHD}
(Rhesus) genes result in the absence of the A, B and D antigens from red cells and other tissues\textsuperscript{1,2}. These LoF variants are important in matching blood for transfusion and for instance, fetuses of D-negative pregnant women are at risk of haemolytic disease. Genome-wide association studies have shown that common variants at \textit{ABO} and \textit{RHD} are associated with the risk of several diseases, as well as, being associated with blood cell traits\textsuperscript{3,4}. In contrast, rare LoF variants in a few blood group genes, when present in homozygosity or compound heterozygosity, are causal of extremely rare inherited diseases\textsuperscript{1}.

Changes in lifestyle, coupled with a genetic component, have led to a steep increase in obesity and associated pathologies rates\textsuperscript{5}. Here, we characterised individuals homozygous for the 17bp deletion in \textit{SMIM1} (rs566629828), who lack the SMIM1 protein from all tissues (hereafter \textit{SMIM1}⁻⁻), and their red cells have no detectable Vel antigen (Fig.S1)\textsuperscript{6–8}. We identified 104 participants with this genotype in 488,376 UK Biobank (UKB) participants, 90 being unrelated and of European ancestry\textsuperscript{9} (46 females and 44 males; Methods and Fig.S2, Table S1), corroborating the previously reported minor allele frequency (MAF) for this deletion in this population\textsuperscript{6} and thus estimating the number of \textit{SMIM1}⁻⁻ individuals at around 150,000 in Europe alone. The 17bp deletion is in high linkage disequilibrium (\textit{D'} 0.98) with the minor (G) allele of rs1175550 (MAF 0.23), a strong sentinel eQTL for \textit{SMIM1} in the blood\textsuperscript{10,11} (www.eqtlgen.org) and associated with red cell traits independently of rs566629828 (Fig.S1).

Interestingly, leveraging on the richness of data in the UKB cohort, we were able to associate \textit{SMIM1}⁻⁻ participants with increased weight (linear regression, Fig.1A, Fig.S2 and Table S1). This analysis indicated an autosomal recessive effect, therefore we considered only \textit{SMIM1}+/+ and -/- individuals for the subsequent analyses. These showed further association with body mass index (BMI), waist circumference and both arms’ fat mass (Fig.1B). The effect sizes ($\hat{\beta}$) estimated from UKB measurements ranged between 0.22 and 0.27 standard deviations (sd) with all FDR values below 0.05 (Table S1). For weight, these differences equate to an average extra 4.6kg in females and 2.4kg in males (Table S1). Analysis of UKB plasma biochemistry assays showed that \textit{SMIM1}⁻⁻ participants had greater levels of triglycerides (TG; $\hat{\beta}$=0.3 FDR=1.07e-2; Fig.1B and 1C). Furthermore, they exhibited greater average levels of
liver enzymes with $\beta$ for alanine and aspartate aminotransferase (ALT and AST) of 0.50, and 0.43 and for gamma-glutamyl transferase (GTT) of 0.35 (FDR: 4.10e-06, 5.01e-05 and 2.49e-03, respectively), as well as increased urate levels ($\beta=0.35$, FDR=3.54e-04; Fig.1B and 1C, Table S1). Regression analysis, adjusting for the effects of BMI, removed the associations with body composition features. However, the associations with TG, liver enzymes and urate levels were only attenuated (Fig.1C and Table S1), suggesting that these effects were not solely dependent on BMI. Interestingly, we identified also sex-specific effects. SMIM1/- female UKB participants exhibit greater average fat-free mass in arms and legs (right arm $\beta=0.39$, FDR=2.39e-02; right leg $\beta=0.33$, FDR=6.01e-02; Table S1) and lower average sex hormone binding globulin levels (SHBG; $\beta=-0.41$, FDR=2.93e-2). Additional sex-specific differences were noted and are presented in Table S1. Smim1 knock-out (Smim1/-) mice recapitulated the increased weight observed in UKB. Smim1/- females weight trajectories over time were, on a chow diet, steeper than those of their control littermates already in the first 30 weeks (Fig.1D; linear regression, $\beta=0.53$, P=2.52e-2; Table S2). The effects in males, albeit showing a similar trend, were not significant in the timeframe analysed (Fig.1D).

Importantly, (i) none of the above associations were detected in carriers (single copy) of the 17bp deletion; (ii) none of the above associations were detected for the common eQTL variant rs1175550, suggesting that the metabolic differences were unlikely to be mediated by rs1175550-associated variation in the expression of SMIM1 in red cells\textsuperscript{11}; (iii) even when we observed differences between SMIM1+/+ and +/- individuals, the mean values for the two groups were within the normal ranges for each measurement, (iv) no association was found between SMIM1/- and fasting glucose levels in the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) results\textsuperscript{12}.

To further investigate these findings, we made home visits to obtain blood samples and health data from 25 British SMIM1/- individuals (12 females, 13 males; not UKB participants, Fig.S2) for an extensive survey of metabolism relevant analytes, with results being compared with 180 individuals (100 females, 80 males) who carried at least one reference allele for variant rs566629828; both groups were registered donors with NHS Blood and Transplant (NHSBT; all values in Table S3). We observed the same trend for SMIM1/- individuals to be heavier but, possibly, because of the small
sample size, the significance threshold was not reached (Table S4). We replicated the
associations between SMIM1-/- for increased average levels for ALT and AST with the
same order of magnitude as observed in UKB (Fig.2, Table S4). We also found
associations between SMIM1-/- and increased leptin to adiponectin ratio (LAR;
\( \hat{\beta} = 0.53, \text{FDR}=2.58\times10^{-2} \)), and an increase in free fatty acids (FFA; \( \hat{\beta} = 1.18, \text{FDR}=1.42\times10^{-6} \)), two indices of increased fat mass and insulin resistance (Fig.2A and
2B)\(^{13,14} \). Moreover, we found that SMIM1-/- individuals have lower average levels of
total triiodothyronine and thyroxine (T3; \( \hat{\beta} = -0.86, \text{FDR}=9.87\times10^{-4}; \) T4; \( \hat{\beta} = -0.74, \text{FDR}=2.84\times10^{-3}; \) Fig.2A and 2B) and that levels of thyroid stimulating hormone (TSH)
seemed to be lower (Table S4).

The above findings prompted us to invite 12 SMIM1-/- individuals belonging to the
NHSBT cohort for a 2-day metabolic assessment (Fig.S2). We estimated the effect of
the absence of SMIM1 on resting energy expenditure (REE; a marker of whole body
metabolic activity) by indirect calorimetry and body mass composition by dual-energy
X-ray absorptiometry (DXA), using a well-established protocol\(^{15} \) (Methods). These
studies showed that SMIM1-/- individuals had a lower REE adjusted for lean mass
(Fig.2C, x-axis; Welch Two Sample t-test; \( P=7.62\times10^{-4}, \text{Table S5} \)), whilst there were
no differences in average lean mass compared to 310 unselected controls (Table S5).
Average free T3, but not free T4, measurements were lower in the 12 SMIM1 -/- than
in the controls group (Table S3 and S4) and changes in physique seen in the 90
SMIM1-/- UKB participants were reflected in abnormal body composition visualised by
DXA scans (Fig.2D). Because of the effect on REE and T3 and T4 levels, we explored
the possible involvement of SMIM1 in the hypothalamic-pituitary-thyroid axis\(^{16} \). We
analysed the single-cell RNA-sequencing data in studies that dissected the transcript
levels of these tissues in multiple organisms. In the mouse hypothalamus\(^{17} \)
(GSE113576), Smim1 was expressed at low levels in mature oligodendrocytes and
some, but not all, inhibitory neurons (Fig.S3A). Its expression was largely non-
overlapping with that of the thyrotropin-releasing hormone (TRH; Fig.S3B). In the
human anterior pituitary gland\(^{18} \) (GSE142653), SMIM1 was found expressed in
corticotropes, gonadotropes and somatotropes (Fig.S3C). Whilst, in human thyroid
organoids and mouse thyroid\(^{19} \) (GSE163818) low-level expression was detected
mainly in thyrocytes and as yet uncharacterised Flt1-positive cells (Fig.S3C). These
analyses indicate that SMIM1 could play one or more roles in the hypothalamic-pituitary-thyroid axis.

The associations between the genotype at rs566629828 and phenotypes observed in the UKB and NHSBT cohorts were orthogonally validated in 73 Danish SMIM1/- individuals from the Danish Blood Donor Study\(^2{0}(DBDS; 25\) female, 18 male, and 645 controls), and the Copenhagen Hospital Biobank\(^2{1}(CHB; 12\) female, 18 male, and 450 matched controls). Weight data, available only for the DBDS participants, showed, upon bootstrapping analysis (Methods; controls matched by age, sex and smoking status), consistent directionality for female SMIM1/- individuals. However, the low number of Danish SMIM1/- individuals and a less evident effect on weight in males (Fig.1B) limited the statistical power to detect differences. Interestingly, 20 of the 73 (27\%) SMIM1/- individuals in the Danish cohorts were assigned a diagnosis of disorders of lipoprotein metabolism versus only 13\% in the controls (OR=4.07, FDR=2.09e-04). A review of all prescriptions in both cohorts showed greater use of statins in individuals lacking SMIM1 versus controls (OR=2.36, FDR=2.22e-02; Table S6) indicating a high level of individuals considered 'at risk' of cardiovascular events.

Interestingly an exploratory analysis of hospital episode statistics revealed an increased risk for cerebral events, with 5 cerebral bleeds and 5 thrombotic strokes in the 65 SMIM1/- UKB participants for whom data were available (OR=5.53 and 3.46, FDR=6.88e-04 and 2.32e-02, respectively; Table S7).

In summary, we identified a loss-of-function variant which is present in homozygosity in 1 in 5,000 individuals in Great Britain and with even higher frequency in the Nordic countries (this manuscript and reference\(^7\)). The MAF of rs566629828 is at the interface between common and rare variation, and has one of the largest effects on weight (\(\hat{\beta}=0.22\)) and BMI (\(\hat{\beta}=0.27\)) reported so far with the exception of extremely rare variants directly implicated in lipid metabolism\(^2{2}\). Our findings show that SMIM1/- individuals (Vel negative blood group) exhibit a combination of metabolic features including increased fat mass, inflammation, triglycerides and altered lipoprotein metabolism due, at least in part, to reduced energy expenditure, a major risk factor in obesity\(^2{3,24}\). Some of these associations, like urate and GGT, were driven by the effect being stronger in one sex; others, like SHBG and LDL, were found only in one of the two sexes, females and males respectively. In the more extreme cases, these effects
Stefanucci et al

could lead to insulin resistance and metabolic syndrome accompanied by increased susceptibility to cardiovascular disease, as is supported by analysis of electronic hospital records, which indicated that these individuals may be more prone to cerebral bleeds and thrombotic stroke. All together the observed metabolic phenotype and increased risk for cardiovascular events is compatible with the notion that the absence of the SMIM1 protein results in a state of mild hypothyroidism.

The quantity of genomic data available, including blood donors typed by arrays, is growing rapidly, as is the number of individuals identified as SMIM1-/--. Future studies should investigate how adverse metabolic phenotype and pituitary-thyroid axis abnormalities are linked to the deficiency of this small, transmembrane protein of unknown function, and whether thyroid hormone supplementation can reverse cardiometabolic risk associated with this unique condition.

Methods

A total of 188 SMIM1-/- individuals (101 females, 87 males) from four different cohorts (UKB, NHSBT, DBDS, CHB) were included in the study. For an overview of the cohorts, see Fig.S2.

UK Biobank

The UKB analyses have been conducted under application number 13745. The UKB cohort consists of 502,682 participants, aged between 40 and 69 years of age on enrollment, recruited at 22 assessment centres across the UK between 2006 and 2010. DNA samples were taken from participants and genotyped using the UK Biobank Axiom Array on the GeneTitan (Affymetrix, Santa Clara, CA). Genotype calling and quality control of the UKB dataset have been extensively documented elsewhere.

The UKB Axiom Array contains DNA probes for direct genotyping of the variant underlying the 17bp deletion in SMIM1 (NC_000001.11:g.3775437_3775453del, rs566629828). The specific DNA probes used (Probeset ID: AX-86577342, Variant ID: Affx-80267180) for detection of the deletion have shown high specificity and the rare variant can be reliably called. For this study, only directly measured genotypes for variant rs566629828 were used to identify UKB participants homozygous for the 17bp
deletion in \textit{SMIM1}, as opposed to imputed genotypes (see below). Additionally, manual inspection of genotype call plots for the deletion probeset (AX-86577342) was performed for each of the 106 genotyping batches of 4,700 UKB samples. The linkage disequilibrium score D’ value between variants rs1175550 and rs566629828 was calculated using PLINK software\textsuperscript{26}. The clinical phenotypes have been defined according to the Hospital Episode Statistics (HES) recorded for the majority of UKB participants. The list of ICD-10 codes and fields used to select the cases and traits is in Table S8.

\textbf{NHSBT cohort}

All NHSBT blood donors for this study were recruited under approval 12/EE/0040 by the Research Ethics Committee East of England. Initially, the \textit{SMIM1}/-/- individuals in the NHSBT cohort of blood donors were identified by the testing approach outlined in an earlier publication\textsuperscript{6}. In short, the red cells of a small fraction of the 2 million donations collected annually are tested by haemagglutination for the presence of the Vel blood group antigen with a polyclonal anti-Vel typing reagent. The red cells from donors with a negative result are tested by a confirmatory haemagglutination test using additional anti-Vel typing reagents. If the results of the confirmatory test is again negative then a genotyping test for variant rs566629828 is applied to determine whether the 17bp deletion at rs566629828 is present on both alleles. Currently (December 2021) 141 \textit{SMIM1}/-/- donors are registered on NHSBT’s donor database (66 females, 75 males). Of these, 25 participated in this study by providing samples and relevant health information obtained during a home visit. 12 of the 25 attended the NIHR Clinical Research Facility at Cambridge University Hospitals (Cambridge, UK) for a 2-day metabolic assessment. The measurement results of the \textit{SMIM1}/-/- donors were compared with the results obtained for 180 NHSBT donors (100 females, 80 males) with a reference/reference or reference/alternate genotype for variant rs566629828 as determined by whole-genome sequencing\textsuperscript{27}.

\textbf{DBDS and CHB cohorts}

The CHB participants were recruited under the NVK-1708829, P-2019-93 approval and the DBDS participants were recruited under the 1-10-72-95-13, NVK-1700407, P-2019-99 approval. The CHB participants have been enrolled at the Copenhagen University Hospital and general hospitals in the Zealand region of greater
Copenhagen. Inclusion in the study is limited to patients attending to these hospitals and from whom a blood sample is drawn for ABO and D grouping and/or red cell antibody screening. The cohort is therefore strongly skewed towards patients with medical conditions associated with a high likelihood of requiring transfusion (e.g. surgery, chemotherapy and pregnancy). The DBDS cohort of Danish blood donors is in demographics similar to the cohort of NHSBT blood donors from whom 25 British SMIM1-/- individuals were drawn.

The DNA samples from the 90,000 DBDS and 90,700 CHB participants were genotyped at deCODE Genetics (Reykjavik, Iceland) using the Infinium Global Screening Array (Probeset ID: GSA-24v1-0_C2, v1.0). Imputation of the 17bp deletion rs566629828 was performed by deCODE Genetics using their North European sequencing panel of 15,576 individuals (including 8,429 Danes) as reference. Based on these two imputed datasets, 49 and 34 individuals were identified in DBDS and CHB, with a high likelihood of being homozygous for the 17bp deletion in SMIM1, respectively. The DBDS and CHB participant and genotyping data are linked to the Danish Laboratory Database (DLD), the Danish National Patient Registry (NPR) and the Danish Prescription Database (DPD). These linked databases were used for the association analysis performed for this study.

**Confirmation of rs566629828 genotype status**

Considering the limited accuracy of imputation to determine the genotype of low-frequency variants, and particularly of indels, the genotype at rs566629828 was confirmed by an orthogonal test using DNA extracted from 49 DBDS and 34 CHB blood samples, which were retrieved from the respective sample repositories. In short, DNA was amplified by primers flanking the 17bp deletion in SMIM1 exon 3 (Fig.S1). The amplicons were resolved by agarose gel electrophoresis and visual inspection of the amplicon length (reference and alternate alleles being 178bp and 161bp in length, respectively). Discordant results between the genotype inferred by imputation and the PCR-genotyping test results were observed for 10 DNA samples (DBDS, n=6; CHB, n=4). These ambiguities were resolved by Sanger sequencing of the SMIM1 coding exons 3 and 4 confirming that all 10 discordances were caused by erroneous imputation results. All together 43 and 30 confirmed SMIM1-/- individuals were identified in the DBDS and CHB cohorts, respectively (Fig.S2). Controls are drawn
from the same cohorts in a ratio 15:1, gender and age matched (DBDS, n=645; CHB, n=450). The genotype of the controls was imputed and it was either reference/reference or reference/alternate for the variant rs566629828.

**Statistical analysis**

Linear regression was performed to estimate the effect of continuous variables. The mathematical model used as covariates age, sex and BMI. Where specified, sex and BMI were removed from the equation on occasions. Similarly, for categorical variables, the explanatory effect of variant rs566629828 was estimated by logistic regression. For continuous traits, inverse normal transformation (R package RNOmni) was adopted to normalise the measurements. In the Danish cohorts, the logistic regression analysis was performed with the response variable defined as the presence of an abnormal Nomenclature for Properties and Units (NPU)-code measurement in the DLD dataset, presence of a given ICD10/ICD8 record in the NPR dataset, or presence of a specific prescription in the DPD dataset. The explaining variables used were variant rs566629828 genotype, age of the individuals, genetically inferred sex of the individuals (unless cohort was sex-stratified), and in case of mixed cohort analysis, the cohort of a given individual (DBDS/CHB). Since weight data does not follow a normal distribution, a Wilcoxon signed-rank test was used to assess differences in mean weight-based on variant rs566629828 genotype after sex stratification. Bootstrapping was used to assess directionality in mean weights based on the rs566629828 genotype. For each SMIM1/-/ DBDS case, 100 alternate age, sex and smoking status matched control groups were picked at random. The mean weight of each of these 100 alternate controls groups was compared to the case group's mean weight. Directionality of the difference in mean weights was then assessed for each sex separately. Statistical tests have P values corrected with Benjamini–Hochberg procedure with alpha set at 0.05.

**Metabolic characterisation**

The Cambridge Central East of England Research Ethics Committee approved the study protocol for participants' metabolic characterisation (06/Q0108/84). Volunteers were asked to refrain from exercise, consume alcohol and caffeine for 24 hours before arrival. Each of the 12 participants arrived at the NIHR Clinical Research Facility at Cambridge University Hospitals at 14:00 hours on day 0 and remained until noon on
day 1. Resting energy expenditure (REE) was measured upon waking after an
overnight fast by indirect calorimetry (GEM Nutrition) using a ventilated hood. Gas
analysis exchange measurements were converted into energy equivalents using
calculations by Elia and Livesey\(^\text{32}\). The procedure and precision values of the indirect
calorimetry method have been previously described\(^\text{33}\). Whole-body fat, lean and bone
mass body composition measurements were performed by Dual Energy X-Ray
Absorptiometry (DXA). For the volunteers homozygous for the 17bp deletion in
\textit{SMIM1}, GE Lunar iDXA (Encore version 18) was used for fat mass, lean mass and
bone mineral content (BMC) measurements. For the controls, there was a combination
of GE Lunar iDXA measurements and GE Lunar Prodigy measurements (Encore
version 16). Therefore, all relevant measurements were converted by cross-calibration
equations\(^\text{34}\) to comparable iDXA values before collating and using regression
modelling. Lean mass and REE Z scores were derived by multiple regression
modelling\(^\text{15}\). The coefficients were updated in line with an upgrade in DXA scanner
(REE (kJ/min) = age; -0.015, fat mass (kg); 0.019, lean mass (kg); 0.063, intercept;
1.580, lean mass (kg) = gender (0; male, 1; female); -6.272, height\(^2\) (m\(^2\)); 6.684, bone
mass (kg); 10.458, fat mass (kg); 0.166, intercept; 0.888).

\textbf{Single-cell RNA-seq analyses}

We analysed single-cell RNA-sequencing data from the following sources:

- Mouse hypothalamus (GSE113576)\(^\text{17}\)
- Human fetal pituitary (GSE142653)\(^\text{18}\), human in Fig. S3E
- Mouse pituitary (GSE120410)\(^\text{35}\), mouse in Fig. S3E
- Mouse pituitary (GSE146619)\(^\text{36}\), mouse in Fig. S3E
- Rat pituitary (GSE132224)\(^\text{37}\), rat in Fig. S3E
- Mouse thyroid organoids (GSE163818)\(^\text{19}\)

Normalisation, visualisation, and standard processing of datasets was done through
Seurat\(^\text{38}\). For label transfer of mouse and rat pituitary datasets from the human pituitary
reference: mouse and rat genes were first converted to their human homologs (as
obtained via BioMart\textsuperscript{39}, and ambiguously annotated genes were filtered out, prior to cross-species integration.

**Mice**

C57BL/6N-Smim1<em2(IMPC)Wtsi>/Wtsi heterozygous mice were obtained from the Wellcome Sanger Institute (Cambridge, UK). Animals were housed in a temperature-controlled room (22°C) with a 12-hour light/dark cycle with 55% relative humidity. Food and water were available ad libitum. This research has been regulated under the Animals (Scientific Procedures) Act 1986 Amendment Regulations 2012 following ethical review by the University of Cambridge Animal Welfare and Ethical Review Body (AWERB) and Medical Research Council (MRC) ARES animal facility, under pathogen-free conditions and housed according to UK Home Office guidelines.

**Code availability**

The code used to analyse the cohorts is available at https://github.com/stefanucci-luca/vel_ko_analysis

**Acknowledgements**

We would like to thank: all participants in this study, the NIHR Cambridge Clinical Research Facility, the Wellcome Trust-MRC Institute of Metabolic Science Translational Research Facility and the NIHR BioResource. We thank the National Institute for Health Research, NHS Blood and Transplant, and Health Data Research UK as part of the Digital Innovation Hub Programme. L.S. was a PhD student supported by the British Heart Foundation Cambridge Centre for Research Excellence (RE/18/1/34212). S.V. is supported by the British Heart Foundation (RG/18/7/33636). A.V.P. is supported by the British Heart Foundation (RG/18/7/33636) and the Medical Research Council (MRC_MC_UU_12012/5/RCUK). NS and KC are funded by the Wellcome Trust (219496/Z/19/Z & 210755/Z/18/Z). W.H.O. is an NIHR senior investigator and receives funding from the British Heart Foundation, International Society on Thrombosis and Haemostasis, MRC, NIHR and Thermo Fisher Scientific. J.R.S. and M.L.O. are supported by the Swedish Research Council (2019-01683) and governmental university healthcare grants (ALF-4456521). M.L.O. is a Knut and Alice Wallenberg Clinical Scholar (2014.0312, 2020.0234). D.V. is a member of the MRC Centre for Environment and Health, currently funded by the Medical Research Council
Stefanucci et al (MR/S019669/1, 2019-2024). M.F. is supported by the British Heart Foundation (FS/18/53/33863) and the British Heart Foundation Cambridge Centre for Research Excellence (RE/18/1/34212).

Authors contribution

L.S. and C.M. analysed data and wrote the manuscript. A.R.T. collected samples and performed the mouse work. S.V. performed the mouse work. N.S.G. analysed data and reviewed the genotype calls. L.P.E.W. supervised clinical research facility data collection and analysed data. J.E.K. analysed single cell datasets. F.B and S.F. collected samples. J.C. analysed the glucose level data. U.V. analysed the eQTL data. K.B. and P.B. supervised the plasma biochemistry assays. J.W. performed histopathology. L.W., J.O., A.F., K.R., S.E.A., J.P., G.B. and H.J. organised and performed the NHSBT donors recruitment and sample collection. W.N.E. and G.J.H. analysed the pathology samples. N.S. provided advice for the mouse work and data interpretation. C.E., K.R., M.D. and H.U. supervised the establishment of the Danish cohort. A.S. analysed the clinical research facility data. K.S. supervised the genotyping of the Danish cohorts. V.A. and M.V. provided advice with data interpretation. O.A.B. supervised single cell RNA sequencing data analysis. A.V.P. supervised mouse work. S.R.O. supervised the Danish cohorts analysis. W.J.A. provided statistical analysis supervision. J.R.S. helped with the Danish cohort genotyping validation and advised on analysis. M.I.O., O.B.P. and W.H.O. provided supervision, planned analyses, contributed to data interpretation and wrote the manuscript. K.C. supervised the clinical research facility metabolic characterisation. D.V. provided statistical analysis supervision. M.F. was responsible for project organisation, funds, supervision, experimental and analysis planning, and wrote the manuscript. All authors approved the final version of the manuscript.

References

1. Daniels, G. Human Blood Groups. (John Wiley & Sons, 2008).

2. Gleadall, N. S. et al. Development and validation of a universal blood donor genotyping platform: a multinational prospective study. Blood Adv 4, 3495–3506 (2020).

3. Vuckovic, D. et al. The Polygenic and Monogenic Basis of Blood Traits and Diseases.
Stefanucci et al

410  Cell **182**, 1214–1231.e11 (2020).

411  4. Dahlén, T. *et al.* An agnostic study of associations between ABO and RhD blood group
412    and phenome-wide disease risk. *Elife* **10**, (2021).

413  5. Heitkamp, M. *et al.* Obesity Genes and Weight Loss During Lifestyle Intervention in
414    Children With Obesity. *JAMA Pediatr.* **175**, e205142 (2021).

415  6. Cvejic, A. *et al.* SMIM1 underlies the Vel blood group and influences red blood cell
416    traits. *Nat. Genet.* **45**, 542–545 (2013).

417  7. Storry, J. R. *et al.* Homozygosity for a null allele of SMIM1 defines the Vel-negative
418    blood group phenotype. *Nat. Genet.* **45**, 537–541 (2013).

419  8. Ballif, B. A. *et al.* Disruption of SMIM1 causes the Vel- blood type. *EMBO Mol. Med.* **5**, 
420    751–761 (2013).

421  9. Bycroft, C. *et al.* The UK Biobank resource with deep phenotyping and genomic data.
422    *Nature* **562**, 203–209 (2018).

423  10. Fehrmann, R. S. N. *et al.* Trans-eQTLs reveal that independent genetic variants
424    associated with a complex phenotype converge on intermediate genes, with a major
425    role for the HLA. *PLoS Genet.* **7**, e1002197 (2011).

426  11. Võsa, U. *et al.* Large-scale cis- and trans-eQTL analyses identify thousands of genetic
427    loci and polygenic scores that regulate blood gene expression. *Nat. Genet.* **53**, 1300–
428    1310 (2021).

429  12. Chen, J. *et al.* The trans-ancestral genomic architecture of glycemic traits. *Nat. Genet.* 
430    **53**, 840–860 (2021).

431  13. Finucane, F. M. *et al.* Correlation of the leptin:adiponectin ratio with measures of insulin
432    resistance in non-diabetic individuals. *Diabetologia* **52**, 2345–2349 (2009).

433  14. Gastaldelli, A. *et al.* Role of Adipose Tissue Insulin Resistance in the Natural History of
434    Type 2 Diabetes: Results From the San Antonio Metabolism Study. *Diabetes* **66**, 815–
435    822 (2017).

436  15. Watson, L. P. E. *et al.* An approach to quantifying abnormalities in energy expenditure
437    and lean mass in metabolic disease. *Eur. J. Clin. Nutr.* **68**, 234–240 (2014).
16. Fekete, C. & Lechan, R. M. Central regulation of hypothalamic-pituitary-thyroid axis under physiological and pathophysiological conditions. *Endocr. Rev.* **35**, 159–194 (2014).

17. Moffitt, J. R. *et al.* Molecular, spatial, and functional single-cell profiling of the hypothalamic preoptic region. *Science* **362**, (2018).

18. Zhang, S. *et al.* Single-cell transcriptomics identifies divergent developmental lineage trajectories during human pituitary development. *Nat. Commun.* **11**, 5275 (2020).

19. Romitti, M. *et al.* Single-cell trajectory inference guided enhancement of thyroid maturation in vitro using TGF-beta inhibition. *bioRxiv* 2021.01.18.427103 (2021) doi:10.1101/2021.01.18.427103.

20. Hansen, T. F. *et al.* DBDS Genomic Cohort, a prospective and comprehensive resource for integrative and temporal analysis of genetic, environmental and lifestyle factors affecting health of blood donors. *BMJ Open* **9**, e028401 (2019).

21. Sørensen, E. *et al.* Data Resource Profile: The Copenhagen Hospital Biobank (CHB). *Int. J. Epidemiol.* **50**, 719–720e (2021).

22. Akbari, P. *et al.* Sequencing of 640,000 exomes identifies GPR75 variants associated with protection from obesity. *Science* **373**, (2021).

23. Roberts, S. B. *et al.* Energy expenditure and intake in infants born to lean and overweight mothers. *N. Engl. J. Med.* **318**, 461–466 (1988).

24. Ravussin, E. *et al.* Reduced rate of energy expenditure as a risk factor for body-weight gain. *N. Engl. J. Med.* **318**, 467–472 (1988).

25. Sudlow, C. *et al.* UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* **12**, e1001779 (2015).

26. Purcell, S. *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* **81**, 559–575 (2007).

27. Chen, L. *et al.* Genetic Drivers of Epigenetic and Transcriptional Variation in Human Immune Cells. *Cell* **167**, 1398–1414.e24 (2016).
28. Di Angelantonio, E. et al. Efficiency and safety of varying the frequency of whole blood donation (INTERVAL): a randomised trial of 45 000 donors. *Lancet* **390**, 2360–2371 (2017).

29. Schmidt, M. et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin. Epidemiol.* **7**, 449–490 (2015).

30. Van Hout, C. V. et al. Exome sequencing and characterization of 49,960 individuals in the UK Biobank. *Nature* **586**, 749–756 (2020).

31. McCaw, Z. R., et al. Operating characteristics of the rank-based inverse normal transformation for quantitative trait analysis in genome-wide association studies. *Biometrics* **76**, 1262–1272 (2020).

32. Elia, M. & Livesey, G. Energy expenditure and fuel selection in biological systems: the theory and practice of calculations based on indirect calorimetry and tracer methods. *World Rev. Nutr. Diet.* **70**, 68–131 (1992).

33. Watson, L. P. E. et al. Quantifying energy expenditure in childhood: utility in managing pediatric metabolic disorders. *Am. J. Clin. Nutr.* **110**, 1186–1191 (2019).

34. Watson, L. P. E., et al. An Investigation Into the Differences in Bone Density and Body Composition Measurements Between 2 GE Lunar Densitometers and Their Comparison to a 4-Component Model. *J. Clin. Densitom.* **20**, 498–506 (2017).

35. Cheung, L. Y. M. et al. Single-Cell RNA Sequencing Reveals Novel Markers of Male Pituitary Stem Cells and Hormone-Producing Cell Types. *Endocrinology* **159**, 3910–3924 (2018).

36. Ho, Y. et al. Single-cell transcriptomic analysis of adult mouse pituitary reveals sexual dimorphism and physiologic demand-induced cellular plasticity. *Protein Cell* **11**, 565–583 (2020).

37. Fletcher, P. A. et al. Cell Type- and Sex-Dependent Transcriptome Profiles of Rat Anterior Pituitary Cells. *Front. Endocrinol.* **10**, 623 (2019).

38. Hao, Y. et al. Integrated analysis of multimodal single-cell data. *Cell* **184**, 3573–3587.e29 (2021).
39. Durinck, S. et al. BioMart and Bioconductor: a powerful link between biological databases and microarray data analysis. *Bioinformatics* **21**, 3439–3440 (2005).
Tables index

Table S1 | Linear regression outcomes in the UKB cohort for the traits of interest.
This table contains the trait tested (feature) and the effect size (effect) of SMIM1 -/- on each trait. Standard deviation (sd); confidence intervals (CI); p.value corrected with the Benjamini-Hochberg procedure (p.val.FDR). The Tabs contains the values for the effect not corrected for BMI (no BMI correction) and corrected for the effect of BMI on the traits of interest (BMI corrected). Also, the cohort was stratified by sex and the different results for the strata have been reported in different tabs. Tabs with “sex” label refer to the analysis that uses the whole cohort (i.e. not sex-stratified), but corrected for the effect of sex. On the first tab of this table there is a short demographic description of the UKB cohort, SMIM1-/- and SMIM1+/+ used for this study.

Table S2 | Mice raw data. Characteristics of the Smim1 -/- and +/- littermates used in Fig.1D.

Table S3 | Raw data collected in the NHSBT cohort. The first tab has the cohort characteristics and biochemistry raw data collected from the NHSBT cohort. Body mass index (BMI), leptin to adiponectin ratio (LAR), cholesterol (CHOL), triglycerides levels (TG), high-density lipoprotein (HDL), alanine aminotransferase (ALT), leptin (LEPT), adiponectin (ADPN), aspartate aminotransferase (AST), C reactive protein (hsCRP), free fatty acids (FFA), thyroid-stimulating hormone (TSH), low-density lipoproteins (LDL), triiodothyronine (T3), thyroxine (T4). The second tab has the free T3 and free T4 measurements for a subset of the cohort.

Table S4 | Linear regression outcomes in the NHSBT cohort for the traits presented in Table S3. It contains the trait tested (feature) and the effect size (effect) of SMIM1-/- on each trait. Standard deviation (sd); confidence intervals (CI); p.value corrected with the Benjamini-Hochberg procedure (p.val.FDR). The Tabs contains the values for the effect not corrected for BMI (no BMI correction) and corrected for the effect of BMI on the traits of interest (BMI corrected). Also, the cohort was stratified by sex and the different results for the strata have been reported in different tabs. Tabs with “sex” label refers to the analysis that uses the whole cohort (i.e. not gender stratified) but corrected for the effect of gender.
Table S5 | **Resting energy expenditure (REE) raw data in the NHSBT cohort.** lean mass (LM). Both REE and LM have been reported as Z scores.

Table S6 | **Statistical analysis in the DBDS and CHB cohorts.** (cohort tab) Characteristics data for DBDS and CHB cohorts. (Weight male/female tabs) Test for differences in average weight based on SMIM1 genotypes. (NPR not sex-stratified, male and female tabs) Logistic regression of the effect of SMIM1 genotype on the diagnosis of Ischaemic heart disease, Hyperthyroidism, Diabetes and Obesity. (DPD tab) Logistic regression for the effect of SMIM1 genotypes on prescriptions for Cardiovascular disease, Hypertension, Diabetes and Metabolism. (ICD10) and (ICD8) International Classification of Diseases diagnosis code groups. (p.val) p.value, (glm_OR) Odds ratio, (CI_high) and (CI_low) 95% confidence intervals, (N.total.pos) and (N.total.neg) total number of SMIM1+ positive and SMIM1/- in a given analysis. (N.prescription.pos) and (N.prescription.neg) the total number of individuals with or without a given prescription in a given analysis. (N.diag.pos) and (N.diag.neg) the total number of individuals with or without a given diagnosis in a given analysis. (gender) genders included in a given analysis. (covariates) the covariates included in a given analysis. (N male) and (N female) number of males or females in each cohort, (age male) and (age female) average age of the males or females in each cohort. (sex-fraction) fraction of females to males in a given cohort. (mean SMIM1+) and (mean SMIM1/-) the mean weight of each SMIM1 genotype group. (cohort) the cohort affiliation of a data point or analysis, either DBDS, CHB or both. (p.val wilcoxon) p.value of Wilcoxon signed-rank test for a difference in mean weight between the DBDS SMIM1 genotype groups. (feature) The general condition type being investigated. (prescriptions) The types of prescriptions grouped in the analysis. (ATC) the ATC classification codes of each prescription group.

Table S7 | **Generalised linear regression in the UKB cohort for the diseases of interest.** This table contains the disease tested (Disease) and the effect size (effect (OR)) of SMIM1/- on each trait. Odds ratio (OR); standard deviation (sd); confidence intervals (CI); p.value corrected with the Benjamini-Hochberg procedure (p.val.FDR). Disease traits have been defined according to the HES and ICD-10 codes reported in Table S9. The effect of the SMIM1/- have been corrected for the BMI (tab “Corrected for BMI”)

19
Table S8 | **UKB fields and phenotype definitions used in the analysis of the UKB cohort.** The tab “Fields extracted from UKB” contains the list of fields that have been used in the characterisation of the UKB cohort. The tab "matrix_ICD10_Phenotype" contains the information regarding the ICD-10 codes that have been used to define a disease.
Fig. 1

A

Female

Weight

Male

UKB cohort

SMIM1+/

SMIM1+/

SMIM1-/

B

BMI

Waist Circumference

TG

ALT

AST

GGT

Urate

C

Weight

BMI

Waist circumference

Arm fat left

Arm fat right

TG

ALT

AST

GGT

Urate

D

Mouse genotype

Smim1+/+

Smim1-/

Female

Male

Body weight (g)

Age (weeks)
Fig. 1 | Differences between SMIM1+/+ and SMIM1-/- individuals in the UKB cohort and Smim1-/- knockout mice. (A) Box plots for UKB participants weight (kg) grouped according to their genotype. Sex-stratified data have are shown for the three genotype groups, with females on the left and males on the right, respectively. Boxplot whiskers indicate the 95% confidence interval. (B) Box plots for BMI, waist circumference, and levels of triglycerides (TG), alanine aminotransferase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT) and urate. Boxplot whiskers indicate the 95% confidence interval. (C) Forest plot illustrating the effect size (\( \beta \); percentage of standard deviation) of SMIM1+/+ (blue) versus SMIM1-/- (red) for each trait. Bold characters highlight the measurements that are shown in panel B. Effect sizes corrected for BMI are shown in yellow, and the none corrected ones are in dark grey; \( \beta \) is represented by the dot and the 95% confidence intervals by the horizontal line. (D) Weight trajectories (weight in grams, y-axis; age in weeks, x-axis) comparison between WT (blue) and Smim1 knockout littermates (red), with females (left) and males (right).
Fig. 2

A

|     | FFA  | ALT  | AST  | Ferritin | LAR   | Total T3 | Total T4 |
|-----|------|------|------|----------|-------|----------|----------|
| Unit | µmol/L | U/L | U/L | µg/L | mmol/L | mmol/L | mmol/L |
| Min | 200  | 15   | 25   | 50      | 15    | 50       | 15       |
| Max | 800  | 75   | 75   | 150     | 15    | 200      | 150      |

- • Not Corrected for BMI
- ○ Corrected for BMI

NHSBT cohort

B

Color Mapping (% Fat)
- 25%
- 60%

LAR
- 10
- 15
- 5

Effect size (sd)

C

REE Z-Score
LM Z-Score

D

Color Mapping (% Fat)
- 60%
- 25%
Fig. 2 | Differences between $SMIM1^{+/+}$ and $SMIM1^{-/-}$ individuals in the NHSBT cohort and DXA body scan. (A) Boxplots for free fatty acids (FFA), ALT, AST, ferritin, leptin to adiponectin ratio (LAR), total triiodothyronine (T3), total thyroxine (T4). Boxplot whiskers indicate the 95% confidence interval. (B) Forest plot illustrating the effect size ($\beta$; percentage of standard deviation) of $SMIM1^{+/+}$ versus $SMIM1^{-/-}$ for each trait. Effect sizes corrected for BMI and non-corrected ones are in yellow and dark grey, respectively. $\beta$ is represented by the dot and the 95% confidence intervals by the horizontal line. (C) Scatter plot of Z-scores for resting energy expenditure (REE; x-axis) and lean mass (LM; y-axis). $SMIM1^{+}$ individuals, teal; $SMIM1^{-/-}$ individuals, red. The three $SMIM1^{-/-}$ individuals shown in Fig. 2D are indicated by the black dots with a red circumference. (D) Representative DXA scans showing fat volume and distribution in three $SMIM1^{+}$ participants from the control group (top row, teal borders) and three participants from the $SMIM1^{-/-}$ group (bottom row, red borders).
B

**RDW**

-Log P

Genes

0 20 40 60

Chromosome 1

TP73
TP73-A51
SMIM1
CCDC27
LRRC47
RN7SL574P
CEP104
DFFB

SMIM1 MQQESHVHY SRWEDGSRDG VSLGA/SSTE EASRCRRISQ RLCTGKLQIA MKVLGGVALF WIIFILGYLT GYYVKC

Cytoplasm

Transmembrane

Extracellular

C

**β = -0.04 p = 1.1x10^-60**

**β = 0.15 p = 2.8x10^-51**

rs1175550 genotype

rs566629828 genotype
Fig. S1 | **Associations with red blood cell distribution width at the SMIM1 locus.**

(A) Upper panel: SMIM1 is localised on chromosome 1 at Chr1:p36.23. Middle panel: The genomic region harbouring the SMIM1 gene between coordinates chr1:3,772,749-3,775,982 with the four grey boxes representing the SMIM1 exons, the grey lines being the introns and the arrows in the introns giving the transcript direction. The bright green and red vertical arrows indicate the position of the eQTL variant rs1175550 with an A and G nucleotide being reference and alternate, respectively and of the deletion variant rs566629828 with a reference containing the 17bp sequence of GTCAGCCTAGGGGCTGT and the alternate lacking this sequence, respectively. The distance in base pairs (bp) and the D' value between the two variants are presented above and below the bidirectional horizontal arrow. Lower panel: The predicted sequence of the 78-amino acid (in single letter code) type II SMIM1 protein, with an estimated seven amino acids for the extracellular domain (purple), 23-amino acids for the transmembrane domain (light green) and with the remaining 48-amino acids being cytoplasmic (dark green). The asterisk indicates, on the protein, where the frame changes because of the deletion. (B) Locus zoom plots for SMIM1 (highlighted in green) genomic region showing the 100,000 bp centred on variant rs566629828; the normalised -Log10 P-values for the association between variants and red cell distribution width (RDW) are on the y-axis. The sentinel variant rs1175550 (eQTL variant in blood) is in green; after conditional analysis, it was observed that the 17bp deletion (rs566629828, indicated in red) was independent of the sentinel variant associated with RDW. (C) Effect of the SMIM1 rs1175550 eQTL variant and rs566629828 (17bp deletion) genotypes onto normalised RDW. The two boxplots have RDW distribution (y-axis) by genotype (x-axis). rs1175550 has ref/ref (A/A) in the darkest green, ref/alt (A/G) in green and alt/alt (G/G) in the lightest of green; rs566629828 have SMIM1+/+ in blue, SMIM1+-/- in orange and SMIM1--/- in red. The beta and P-values for the associations are given above the boxplots, note the opposing directionality of the beta values, being negative for the eQTL variant (in blood SMIM1+/+ transcript level in alt/alt > alt/ref > ref/ref) and being positive for the deletion variant. This is in keeping with the observation that lower levels of SMIM1 RNA are associated with higher RDW levels. It is also worthwhile noting that in red cells effects of the eQTL and the 17bp deletion variants are also observed in heterozygous individuals - this is in sharp contrast with the effect of the 17bp deletion on body weight (Fig. 1A).
UKB
All: n=488,376; CEU, 460,186; SAS,EAS, 9,473; AFR, 7,649; CHINESE, 1,504; OTHER, 9,564
SMIM1-/-: n=104

Unrelated Europeans:
n=408,498
Females:Males = 1.2:1.0
SMIM1-/-: n=90 (46,44)
SMIM1+/+: n=396,559

NHSBT
All: n=1.3 million
Females:Males = 1.5:1.0
SMIM1-/-: n=141 (66,75)

Metabolism relevant analytes
SMIM1-/-: n=25 (12,13)
Controls: n=180 (100,80)

NHSBT
2-day metabolic assessment at CRF
SMIM1-/-: n=12 (5,7)
Controls CRF: n=310

DBDS
All: n=90,000
Females:Males = 1.05:1.0
Imputation for rs566629828
SMIM1-/-: n=43 (25,18)
Controls: n=645 (age and sex matched)

CHB
All: n=90,700
Females:Males = 0.98:1.0
Imputation for rs566629828
SMIM1-/-: n=34
Controls: n=450 (age and sex matched)

Confirmation of 17bp deletion for at rs566629828 by PCR for those who accepted to take part in this study

CRF, Cambridge NIHR Clinical Research Facility
Genotype and phenotype data from four cohorts were used for the study. From left to right UK Biobank (UKB), National Health Service Blood and Transplant (NHSBT), Danish Blood Donor Study (DBDS and The Copenhagen Hospital Biobank (CHB). The top row provides the number of participants for whom genotype (Vel phenotype in case of NHSBT cohort) information was available and the female: male ratio. For the UKB the ethnicity of the participants is also provided (data taken from Bycroft et al., 2018)\textsuperscript{10}. The middle row provides the number of \textit{SMIM1-/-} individuals per cohort which were included in the study; between brackets (female/male) individuals.
Fig.S3 | **SMIM1 expression at single-cell resolution in mammalian hypothalamus, pituitary and thyroid.** (A) UMAP representation of the different cell types found in mouse hypothalamus snRNA-seq data (GSE113576). (B) Smim1 and Trh expression levels in the different cell types found in mouse hypothalamus. (C) UMAP representation of the different cell types found in human foetal pituitary scRNA-seq data (GSE142653). (D) SMIM1 and representative genes expression levels in the different cell types found in the human foetal pituitary. (E) Smim1 and representative genes expression levels in the different cell types found in rat and mouse pituitary. (F) Smim1 and representative genes expression levels in the different cell types found in mouse thyroid organoids (GSE163818).
Supplementary author lists

DBDS Genetic Consortium list

Steffen Andersen
Karina Banasik
Søren Brunak
Kristoffer Burgdorf
Maria Didriksen
Khoa Manh Dinh
Christian Erikstrup
Daniel Gudbjartsson
Thomas Folkmann Hansen
Henrik Hjalgrim
Gregor Jemec
Poul Jennum
Pär Ingemar Johansson
Margit Aniita Hørup Larsen
Susan Mikkelsen
Kasper Rene Nielsen
Mette Nyegaard
Sisse Rye Ostrowski
Ole Birger Pedersen
Kari Stefansson
Hreinn Stefánsson
Susanne Sækmose
Erik Sørensen
Stefanucci et al

Unnur Þorsteinsdóttir

Mie Topholm Brun

Henrik Ullum

Thomas Werge

1 Department of Finance, Copenhagen Business School, Copenhagen, Denmark
2 Novo Nordisk Foundation Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
3 Department of Clinical Immunology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark
4 Department of Clinical Immunology, Aarhus University Hospital, Aarhus
5 deCODE Genetics, Reykjavik, Iceland
6 Danish Headache Center, Department of Neurology, Copenhagen University Hospital, Rigshospitalet – Glostrup
7 Department of Epidemiology Research, Statens Serum Institut, Centre for Cancer Research, Danish Cancer Society, Copenhagen, Denmark
8 Department of Clinical Medicine, Sealand University Hospital – Roskilde, Roskilde, Denmark
9 Department of Clinical Neurophysiology, University of Copenhagen, Copenhagen, Denmark
10 Department of Clinical Immunology, Aalborg University Hospital, Aalborg, Denmark
11 Department of Biomedicine, Aarhus University, Aarhus, Denmark
12 Department of Clinical Immunology, Zealand University Hospital – Køge, Køge, Denmark
13 Department of Clinical Immunology, Odense University Hospital, Odense, Denmark
14 Statens Serum Institute, Copenhagen, Denmark
15 Institute of Biological Psychiatry Mental Health Centre, Sct. Hans, Copenhagen University Hospital – Roskilde, Roskilde, Denmark
Stefanucci et al

696 MAGIC contributors list

697 Meta-Analysis of Glucose and Insulin-related Traits Consortium (MAGIC)

698 Ji Chen1,2, Cassandra N. Spracklen3,4, Gaëlle Marenne2,5, Arushi Varshney6, Laura

699 J Corbin7,8, Jian’an Luan9, Sara M Willems9, Ying Wu3, Xiaoshuai Zhang9,10, 

700 Momoko Horikoshi11,12,13, Thibaud S Boutin14, Reedik Mägi15, Johannes

701 Waage16, Ruifang Li-Gao17, Kei Hang Katie Chan18,19,20, Jie Yao21, Mila D

702 Anasanti22, Audrey Y Chu23, Annique Claringbold24, Jani Heikkinen22, Jaeyoung

703 Hong25, Jouke-Jan Hottenga26,27, Shaofeng Huo28, Marika A. Kaakinen29,22, Tin

704 Louie30, Winfried März31,32,33, Hortensia Moreno-Macías34, Anne Ndungu12, 

705 Sarah C. Nelson30, Ilja M. Nolte35, Kari E North36, Chelsea K. Raulerson3,6

706 Debashree Ray37, Rebecca Rohde36, Denis Rybin25, Claudia Schurmann38,39, 

707 Xueling Sim40,41,42, Loz Southam2, Isobel D Stewart9, Carol A. Wang43, Yujie

708 Wang36, Peitao Zhao44,45, Turunveer S. Ahiwalia16,46,47, Emil

709 VR Appel48, Lawrence F. Bielak49, Jennifer A. Brody50, Noël P Burtt51, Claudia P

710 Cabrera52,53, Brian E Cade54,55, Jin Fang Chai40, Xiaoran Chai56,57, Li-Ching

711 Chang58, Chien-Hsiun Chen58, Brian H Chen59, Kumasawamy Naidu Chitra60, 

712 Yen-Feng Chiu61, Hugoline G. de Haan17, Graciela E Delgado33, Ayse

713 Demirkan62,29, Qing Duan3,63, Jorgen Engmann64, Segun A Fatumo65,66,67, 

714 Javier Gayán68, Franco Giuliani69, Jung Ho Gong18, Stefan Gustafsson70, Yang

715 Hai71, Fernando P Hartwig72,7, Jing He73, Yoriko Heianza74, Tao Huang75, Alicia

716 Huerta-Chagoya76,77, Mi Yeong Hwang78, Richard A. Jensen50, Takahisa

717 Kawaguchi79, Katherine A Kentistou80,81, Young Jin Kim78, Marcus E Kleber33, 

718 Ishminder K Kooner45, Shuiqing Lai18, Leslie A Lange82, Carl D Langefeld83, Marie

719 Lauzon21, Man Li84, Symen Ligthart62, Jun Liu62,85, Marie Loh86,44, Jirong

720 Long87, Valeriya Lyssenko88,89, Massimo Mangino90,91, Carola Marzì92,93, May E

721 Montasser94, Abhishek Nag12, Masahiro Nakatochi95, Damia Noce96, Raymond

722 Noordam97, Giorgio Pistis98, Michael Preuss38,99, Laura Raffield3, Laura J. 

723 Rasmussen-Torvik100, Stephen S Rich101,102, Neil R Robertson11,12, Rico

724 Rueedi103,104, Kathleen Ryan94, Serena Sanna98,24, Richa Saxena105,106,107, 

725 Katharina E Schraut80,81, Bengt Sennblad108, Kazuya Setoh79, Albert V 

726 Smith109,110, Lorraine Southam111,112, Thomas Sparsø48, Rona J 

727 Strawbridge113,114, Fumihiko Takeuchi115, Jingyi Tan21, Stella Trompet97,116, 

728 Erik van den Akker117,118,119, Peter J van der Most35, Niek Verweij120,121, Mandy

729 Vogel122, Heming Wang54,55, Chaolong Wang123,124, Nan Wang125,126, Helen

730 R Warren52,53, Wanqing Wen87, Tom Wilsgaard127, Andrew Wong128, Andrew R 

731 Wood1, Tian Xie35, Mohammad Hadi Zafarmand129,130, Jing-Hua Zhao131, Wei

732 Zhao49, Najaf Amin62,85, Zorayr Arzumananyan21, Arne Astrup132, Stephan JL 

733 Bakker133, Damiano Baldassarre134,135, Marian Beekman117, Richard N 

734 Bergman136, Alain Bertoni137, Matthias Blüher138, Lori L. Bonnycastle139, Stefan R 

735 Bornstein140, Donald W Bowden141, Qiuyin Cai73, Archie Campbell142,143, Harry

736 Campbell80, Yi Cheng Chang144,145,146, Eco J.C. de Geus26,27, Abbas 

737 Dehghan62, Shufa Du147, Gudny Einarsdottir110, Ailiki Eleni Farmaki148,149, Mattias
Stefanucci et al.

Frånberg150, Christian Fuchsberger96, Yutang Gao151, Anette P Gjesing48, Anuj Goel152,12, Sohee Han78, Catharina A Hartman153, Christian Herder154,155,156, Andrew A. Hicks96, Chang-Hsun Hsieh157,158, Willa A. Hsueh159, Sahoko Ichihara160, Michiya Igase161, M. Arfan Ikram62, W. Craig Johnson30, Marit E Jørgensen46,162, Peter K Joshi80, Rita R Kalyani163, Fouad R. Kandeel164, Tomohiro Katsuya165,166, Chiea Chuen Khor124, Wieland Kiess122, Ivana Kolcic167, Teemu Kuulasmaa168, Johanna Kuusisto169, Kristi Lääli15, Kelvin Lam21, Deborah A Lawlor170,8, Nanette R. Lee171,172, Rozenn N. Lemaitre50, Honglan Li173, Shih-Yi Lin174,175,176, Jaana Lindström177, Allan Linneberg178,179, Jianjun Liu124,180, Carlos Lorenzo181, Tatsuaki Matsubara182, Fumihiro Matsuda79, Geltrude Mingrone183, Simon Mooijaart97, Sanghoon Moon78, Toru Nabika184, Ghish N. Nadkarni38, Jerry L. Nadler185, Mari Nelis15, Matt J Neville11,186, Jill M Norris187, Yasumasa Ohyagi188, Annette Peters189,93,190, Patricia A. Peyser49, Ozren Polasek167,191, Qibin Qi192, Dennis Raven153, Dermot F Reilly193, Alex Reiner194, Fernando Rivideneira195, Kathryn Roll21, Igor Rudan196, Charumathi Sabanayagam56,197, Kevin Sandow21, Naveed Sattar198, Annette Schürmann199,200, Jinxiu Shi201, Heather M Stringham42,41, Kent D. Taylor21, Tanya M. Teslovich202, Betina Thuesen178, Paul RHJ Timmers80,203, Elena Tremoli135, Michael Y Tsai204, Andre Uitterlinden195, Rob M van Dam40,180,205, Diana van Heemst97, Astrid van Hylckama Vlieg17, Jana V Van Vliet-Oostapchouk35, Jagadish Vangipurapu206, Henrik Vestergaard48,207, Tao Wang192, Ko Willems van Dijk208,209,210, Tatijana Zemunik211, Goncalo R Abecasis42, Linda S. Adair147,212, Carlos Alberto Aguilera-Salinas213,214,215, Marta E Alarcón-Riquelme216,217, Ping An218, Larissa Aviles-Santa219, Diane M Becker220, Lawrence J Beilin221, Sven Bergmann103,104,222, Hans Bisgaard16, Corri Black223, Michael Boehnke42,41, Eric Boerwinkle224,225, Bernhard O Böhm226,227, Klaus Bønnelykke16, D I. Boomsma26,27, Erwin P Bottiger38,228,229, Thomas A Buchananc203,230,231,126, Mickael Canouil232,233,234,235,236, Mark J Caulfield52,53, John C. Chambers86,44,45,234,235, Daniel I. Chasman69,236, Yi-Der Ida Chen21, Ching-Yu Cheng56,197, Francis S. Collins139, Adolfo Correa237, Francesco Cucca98, H. Janaka de Silva238, George Dedoussis239, Sölve Elmhåll240, Michele K. Evans241, Ele Ferrannini242, Luigi Ferrucci243, Jose C Flores244,245,107, Paul W Franks89,246, Timothy M Frayling1, Philippe Froguel232,233,247, Bruna Gigante248, Mark O. Goodarzi249, Penny Gordon-Larsen147,212, Harald Grallert92,93, Niels Grarup48, Sameline Grimsgaard127, Leif Groop250,251, Vilmundur Gudnason110,252, Xiaqing Guo21, Anders Hamsten114, Torben Hansen48, Caroline Hayward203, Susan R. Heckbert253, Bernado L Horta72, Wei Huang201, Erik Ingelsson254, Pankow S James255, Marjo-Ritta Jarvelin256,257,258,259, Jost B Jonas260,261,262, J. Wouter Jukema116,263, Pontiano Kaleebu264, Robert Kaplan192,194, Sharon L.R. Kardia49, Norihiro Kato115, Sirkka M. Keinanen-Kiukaanniemi265,266, Bong-Jo Kim78, Mika Kivimäki267, Heikki A. Koistinen268,269,270, Jaspal S. Koonen45,234,235,271, Antje Körner122, Peter Kovacs138,272, Diana Kühle128, Meena Kumari273, Zoltan Kutalik274,104, Markku Laakso169, Timo A.
of Oxford, Oxford, UK, 13Laboratory for Genomics of Diabetes and Metabolism, RIKEN Centre for Integrative Medical Sciences, Yokohama, Japan, 14Medical Research Council Human Genetics Unit, Institute for Genetics and Molecular Medicine, Edinburgh, UK, 15Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia, 16COPSAC, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark, 17Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands, 18Department of Epidemiology, Brown University School of Public Health, Brown University, Providence, RI, USA, 19Department of Biomedical Sciences, City University of Hong Kong, Hong Kong SAR, China, 20Department of Electrical Engineering, City University of Hong Kong, Hong Kong SAR, China, 21The Institute for Translational Genomics and Population Sciences, Department of Pediatrics, The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA, USA, 22Department of Metabolism, Digestion, and Reproduction, Imperial College London, London, UK, 23Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, USA, 24Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, 25Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA, 26Department of Biological Psychology, Faculty of Behaviour and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands, 27Amsterdam Public Health Research Institute, Amsterdam, The Netherlands, 28CAS Key Laboratory of Nutrition, Metabolism and Food Safety, Shanghai Institute of Nutrition and Health, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai, China, 29Section of Statistical Multi-omics, Department of Clinical and Experimental Research, University of Surrey, Guildford, Surrey, UK, 30Department of Biostatistics, University of Washington, Seattle, WA, USA, 31SYNLAB Academy, SYNLAB Holding Deutschland GmbH, Mannheim, Germany, 32Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University Graz, Graz, Austria, 33Vth Department of Medicine (Nephrology, Hypertension, Rheumatology, Endocrinology, Diabetology), Medical Faculty Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, Germany, 34Department of Economics, Metropolitan Autonomous University, Mexico City, Mexico, 35Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, 36CVD Genetic Epidemiology Computational Laboratory, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA, 37Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, 38The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA, 39HPI Digital Health Center, Digital Health and Personalized Medicine, Hasso Plattner Institute, Potsdam, Germany, 40Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, Singapore, 41Center for Statistical Genetics, University of Michigan, Ann Arbor, MI, USA, 42Department of Biostatistics, School of Public Health,
Stefanucci et al

869 University of Michigan, Ann Arbor, MI, USA, 43School of Medicine and Public Health, 870 College of Health, Medicine and Wellbeing, The University of Newcastle, Newcastle, 871 NSW, Australia, 44Department of Epidemiology and Biostatistics, Imperial College 872 London, London, UK, 45Department of Cardiology, Ealing Hospital, London North 873 West Healthcare NHS Trust, Middlesex, UK, 46Steno Diabetes Center Copenhagen, 874 Gentofte, Denmark, 47The Bioinformatics Centre, Department of Biology, University 875 of Copenhagen, Copenhagen, Denmark, 48Novo Nordisk Foundation Center for Basic 876 Metabolic Research, Faculty of Health and Medical Sciences, University of 877 Copenhagen, Copenhagen, Denmark, 49Department of Epidemiology, School of 878 Public Health, University of Michigan, Ann Arbor, MI, USA, 50Department of Medicine, 879 Cardiovascular Health Research Unit, University of Washington, Seattle, WA, USA, 880 51Metabolism Program, Program in Medical and Population Genetics, Broad Institute, 881 Cambridge, MA, USA, 52Department of Clinical Pharmacology, William Harvey 882 Research Institute, Barts and The London School of Medicine and Dentistry, Queen 883 Mary University of London, London, UK, 53NIHR Barts Cardiovascular Biomedical 884 Research Centre, Queen Mary University of London, London, UK, 54Department of 885 Medicine, Sleep and Circadian Disorders, Brigham and Women's Hospital, Boston, 886 MA, USA, 55Department of Medicine, Sleep Medicine, Harvard Medical School, 887 Boston, MA, USA, 56Ocular Epidemiology, Singapore Eye Research Institute, 888 Singapore National Eye Centre, Singapore, Singapore, 57Department of 889 Ophthalmology, National University of Singapore and National University Health 890 System, Singapore, Singapore, 58Institute of Biomedical Sciences, Academia Sinica, 891 Taipei, Taiwan, Taiwan, 59Department of Epidemiology, The Herbert Wertheim 892 School of Public Health and Human Longevity Science, UC San Diego, La Jolla, CA, 893 USA, 60Laboratory of Epidemiology and Population Sciences, National Institute on 894 Aging, National Institutes of Health, Baltimore, MD, USA, 61Institute of Population 895 Health Sciences, National Health Research Institutes, Miaoli, Taiwan, 62Department 896 of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands, 897 63Department of Statistics, University of North Carolina at Chapel Hill, Chapel Hill, 898 NC, USA, 64Institute of Cardiovascular Science, UCL, London, UK, 65Uganda 899 Medical Informatics Centre (UMIC), MRC/UVRI and London School of Hygiene & 900 Tropical Medicine (Uganda Research Unit), Entebbe, Uganda, 66London School of 901 Hygiene & Tropical Medicine, London, UK, 67H3Africa Bioinformatics Network 902 (H3ABioNet) Node, Centre for Genomics Research and Innovation, NABDA/FMST, 903 Abuja, Nigeria, 68Bioinfosol, Sevilla, Spain, 69Division of Preventive Medicine, 904 Brigham and Women's Hospital, Boston, MA, USA, 70Department of Medical 905 Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala 906 University, Uppsala, Sweden, 71Department of Statistics, The University of Auckland, 907 Science Center, Auckland, New Zealand, 72Postgraduate Program in Epidemiology, 908 Federal University of Pelotas, Pelotas, RS, Brazil, 73Department of Medicine, 909 Epidemiology, Vanderbilt University Medical Center, Nashville, TN, USA, 910 74Department of Epidemiology, Tulane University Obesity Research Center, Tulane 911 University, New Orleans, USA, 75Department of Epidemiology and Biostatistics, 912 School of Public Health, Peking University, Beijing, China, 76Molecular Biology and
Genomic Medicine Unit, National Council for Science and Technology, Mexico City, Mexico, 77Molecular Biology and Genomic Medicine Unit, National Institute of Medical Sciences and Nutrition, Mexico City, Mexico, 78Division of Genome Science, Department of Precision Medicine, National Institute of Health, Cheongju-si, Chungcheongbuk-do, South Korea, 79Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan, 80Centre for Global Health Research, Usher Institute, University of Edinburgh, Edinburgh, Scotland, 81Centre for Cardiovascular Sciences, Queen’s Medical Research Institute, University of Edinburgh, Edinburgh, Scotland, 82Department of Medicine, Division of Biomedical Informatics and Personalized Medicine, University of Colorado Anschutz Medical Campus, Denver, CO, USA, 83Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC, USA, 84Department of Medicine, Division of Nephrology and Hypertension, University of Utah, Salt Lake City, UT, USA, 85Nuffield Department of Population Health, University of Oxford, Oxford, UK, 86Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore, 87Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt University Medical Center, Nashville, TN, USA, 88Department of Clinical Science, Center for Diabetes Research, University of Bergen, Bergen, Norway, 89Department of Clinical Sciences, Lund University Diabetes Centre, Lund University, Malmo, Sweden, 90Department of Twin Research and Genetic Epidemiology, School of Life Course Sciences, King’s College London, London, UK, 91NIHR Biomedical Research Centre, Guy’s and St Thomas’ Foundation Trust, London, UK, 92Institute of Epidemiology, Research Unit of Molecular Epidemiology, Helmholtz Zentrum München Research Center for Environmental Health, Neuherberg, Bavaria, Germany, 93German Center for Diabetes Research (DZD), Neuherberg, Bavaria, Germany, 94Department of Medicine, Division of Endocrinology, Diabetes, and Nutrition, University of Maryland School of Medicine, Baltimore, MD, USA, 95Public Health Informatics Unit, Department of Integrated Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan, 96Institute for Biomedicine, Eurecat Research, Bolzano, BZ, Italy, 97Department of Internal Medicine, Section of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands, 98Istituto di Ricerca Genetica e Biomedica (IRGB), Consiglio Nazionale delle Ricerche (CNR), Monserrato, Italy, 99The Mindich Child Health and Development Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA, 100Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA, 101Center for Public Health Genomics, University of Virginia, Charlottesville, VA, USA, 102Department of Public Health Sciences, University of Virginia, Charlottesville, VA, USA, 103Department of Computational Biology, University of Lausanne, Lausanne, Switzerland, 104Swiss Institute of Bioinformatics, Lausanne, Switzerland, 105Center for Genomic Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, 106Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA, 107Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, USA, 108Department of Cell
Center, Jackson, MS, USA, 238Department of Medicine, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka, 239Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University of Athens, Kallithea, Greece, 240Department of Clinical Sciences, Lund University, Malmö, Sweden, 241Laboratory of Epidemiology and Population Sciences, National Institute on Aging Intramural Research Program, National Institutes of Health, Baltimore, MD, USA, 242CNR Institute of Clinical Physiology, Pisa, Italy, 243Intramural Research Program, National Institute of Aging, Baltimore, MD, USA, 244Diabetes Unit and Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA, 245Department of Medicine, Harvard Medical School, Boston, MA, USA, 246Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden, 247Department of Genomics of Common Disease, Imperial College London, London, UK, 248Department of Medicine, Cardiovascular medicine, Karolinska Institutet, Stockholm, Sweden, 249Department of Medicine, Division of Endocrinology, Diabetes & Metabolism, Cedars-Sinai Medical Center, Los Angeles, CA, USA, 250Diabetes Centre, Lund University, Sweden, 251Finnish Institute of Molecular Medicine, Helsinki University, Helsinki, Finland, 252Faculty of Medicine, School of health sciences, University of Iceland, Reykjavik, Iceland, 253Department of Epidemiology, Cardiovascular Health Research Unit, University of Washington, Seattle, WA, USA, 254Department of Medicine, Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford University, Stanford, CA, USA, 255Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA, 256Department of Epidemiology and Biostatistics, MRC-PHE Centre for Environment and Health, School of Public Health, Imperial College London, London, UK, 257Center for Life Course Health Research, Faculty of Medicine, University of Oulu, Oulu, Finland, 258Unit of Primary Health Care, Oulu University Hospital, OYS, Oulu, Finland, 259Department of Life Sciences, College of Health and Life Sciences, Brunel University London, London, UK, 260Department of Ophthalmology, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany, 261Beijing Institute of Ophthalmology, Beijing Ophthalmology and Visual Science Key Lab, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China, 262Institute of Molecular and Clinical Ophthalmology Basel IOB, Basel, Switzerland, 263Netherlands Heart Institute, Utrecht, The Netherlands, 264MRC/UVRi and LSHTM (Uganda Research Unit), Entebbe, Uganda, 265Faculty of Medicine, Institute of Health Sciences, University of Oulu, Oulu, Finland, 266Unit of General Practice, Oulu University Hospital, Oulu, Finland, 267Department of Epidemiology and Public Health, UCL, London, UK, 268Department of Public Health Solutions, Finnish Institute for Health and Welfare, Helsinki, Finland, 269Department of Medicine, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland, 270Minerva Foundation Institute for Medical Research, Helsinki, Finland, 271National Heart and Lung Institute, Imperial College London, London, UK, 272IFB Adiposity Diseases, University of Leipzig Medical Center, Leipzig, Germany, 273Institute for Social and Economic Research, University of Essex, Colchester, UK, 274University Institute of Primary Care and
Stefanucci et al

1177 Public Health, Division of Biostatistics, University of Lausanne, Lausanne, Switzerland, 275
1178 Institute of Biomedicine, School of Medicine, University of Eastern Finland, Finland, 276
1179 Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland, 277
1180 Foundation for Research in Health Exercise and Nutrition, Kuopio Research Institute of Exercise Medicine, Kuopio, Finland, 278
1181 Institute of Environmental Medicine, Cardiovascular and Nutritional Epidemiology, Karolinska Institutet, Stockholm, Sweden, 279
1182 Department of Medical Sciences, Uppsala, Sweden, 280
1183 Big Data Institute, Nuffield Department of Medicine, University of Oxford, Oxford, UK, 281
1184 Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, UK, 282
1185 Department of Medical Epidemiology and Biostatistics and the Swedish Twin Registry, Karolinska Institutet, Stockholm, Sweden, 283
1186 Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands, 284
1187 Institute of Cardiovascular and Medical Sciences, School of Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK, 286
1188 Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK, 287
1189 Department of Health Services, Cardiovascular Health Research Unit, University of Washington, Seattle, WA, USA, 288
1189 Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA, 289
1190 Department of Pediatrics, Genetic and Genomic medicine, University of California, Irvine, Irvine, CA, USA, 290
1191 Havard Medical School, Boston, MA, USA, 291
1192 Finnish Diabetes Association, Tampere, Finland, 292
1193 Pirkanmaa Hospital District, Tampere, Finland, 293
1194 Department of Medicine, University of Cambridge, Cambridge, UK, 294
1195 South Karelia Central Hospital, Lappeenranta, Finland, 295
1196 Department of Psychology, University of Miami, Miami, FL, USA, 296
1197 Paul Langerhans Institute Dresden of the Helmholtz Center Munich, University of California, Irvine, Irvine, CA, USA, 290
1198 Havard Medical School, Boston, MA, USA, 291
1199 Tampere, Finnish Diabetes Association, Tampere, Finland, 292
1200 Pirkanmaa Hospital District, Tampere, Finland, 293
1201 Department of Medicine, Internal Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland, 309
1202 Department of Public Health Sciences, Wake Forest School of
Stefanucci et al

1221  Medicine, Winston-Salem, NC, USA, 310Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK, 311Beijing Tongren Eye Center, Beijing Key Laboratory of Intraocular Tumor Diagnosis and Treatment, Beijing Ophthalmology & Visual Sciences Key Lab, Beijing Tongren Hospital, Capital Medical University, Beijing, China, China, 312Department of Public Health, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka, 313Department of Research and Evaluation, Kaiser Permanente of Southern California, Pasadena, CA, USA, 314Institute for Molecular Bioscience, The University of Queensland, Queensland, Australia, 315Kurume University School of Medicine, Japan, 316Wellcome Sanger Institute, Hinxton, UK, 317TUM School of Medicine, Technical University of Munich and Klinikum Rechts der Isar, Munich, Germany, 318Department of Pediatrics, Division of Endocrinology, Stanford School of Medicine, Stanford, CA, USA, 319Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK, 320Department of Medicine, Division of General Internal Medicine, Massachusetts General Hospital, Boston, MA, USA, 321Department of Medicine, General Internal Medicine, Massachusetts General Hospital, Boston, MA, USA, 322Department of Medicine, Diabetes Unit and Endocrine Unit, Massachusetts General Hospital, Boston, MA, USA, 323Department of Human Genetics, University of Michigan, Ann Arbor, MI, USA, 324Centre for Genetics and Genomics Versus Arthritis, Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, Manchester, UK, 325Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, Manchester, UK, 326Department of Biostatistics, University of Liverpool, Liverpool, UK, 327University of Cambridge, Cambridge