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\*SHE defined as number of hypoglycaemic events requiring third-party assistance (with or without medical assistance). 1. Puhf S et al. Diabetes Technol Ther. 2019;21(4):155-158. 2. Puhf S et al. J Diabetes Sci Technol. 2020;14(1):83-86. 3. Heinemann L, et al. Lancet 2018;391:1367-1377. Dexcom, Dexcom G6, Dexcom Follow, Dexcom Share, and Dexcom CLARITY are registered trademarks of Dexcom, Inc. in the U.S. and may be in other countries. © 2020 Dexcom International Ltd. All rights reserved. Dexcom International Ltd and its affiliated European entities. This product is covered by U.S. patent. www.dexcom.com | +1.858.200.0200 | Dexcom, Inc. 6340 Sequence Drive San Diego, CA 92121 USA | MDSS GmbH Schiffgraben 41 30175 Hannover, Germany. LBL021139 Rev001.

## RESEARCH: GENETICS

# Genetically defined favourable adiposity is not associated with a clinically meaningful difference in clinical course in people with type 2 diabetes but does associate with a favourable metabolic profile

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## Abstract

**Aims:** Change in weight, HbA<sub>1c</sub>, lipids, blood pressure and cardiometabolic events over time is variable in individuals with type 2 diabetes. We hypothesised that people with a genetic predisposition to a more favourable adiposity distribution could have a less severe clinical course/progression.

**Methods:** We involved people with type 2 diabetes from two UK-based cohorts: 11,914 individuals with GP follow-up data from the UK Biobank and 723 from Salford. We generated a 'favourable adiposity' genetic score and conducted cross-sectional and longitudinal studies to test its association with weight, BMI, lipids, blood pressure, medication use and risk of myocardial infarction and stroke using 15 follow-up time points with 1-year intervals.

**Results:** The 'favourable adiposity' genetic score was cross-sectionally associated with higher weight (effect size per 1 standard deviation higher genetic score: 0.91 kg [0.59,1.23]) and BMI (0.30 kg/m<sup>2</sup> [0.19,0.40]), but higher high-density lipoprotein

Adrian H. Heald, Susan Martin are first authors who contributed equally.

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(0.02 mmol/L [0.01,0.02]) and lower triglycerides (−0.04 mmol/L [−0.07, −0.02]) in the UK Biobank at baseline, and this pattern of association was consistent across follow-up. There was a trend for participants with higher ‘favourable adiposity’ genetic score to have lower risk of myocardial infarction and/or stroke (odds ratio 0.79 [0.62, 1.00]) compared to those with lower score. A one standard deviation higher score was associated with lower odds of using lipid-lowering (0.91 [0.86, 0.97]) and anti-hypertensive medication (0.95 [0.91, 0.99]).

**Conclusions:** In individuals with type 2 diabetes, having more ‘favourable adiposity’ alleles is associated with a marginally better lipid profile long-term and having lower odds of requiring lipid-lowering or anti-hypertensive medication in spite of relatively higher adiposity.

#### KEY WORDS

BMI, ectopic fat, favourable adiposity genetic score, HbA<sub>1c</sub>, metabolic profile, myocardial infarction, stroke, type 2 diabetes

## 1 | INTRODUCTION

Changes in weight, glycated haemoglobin (HbA<sub>1c</sub>), lipids and blood pressure over time display significant variability across individuals with type 2 diabetes, with many and varied determinants including genetic, environmental and lifestyle factors. Weight gain in type 2 diabetes is associated with multiple adverse consequences.<sup>1</sup> Furthermore, long-term follow-up studies have clearly shown a direct relation between the levels of blood pressure, glucose and low-density lipoprotein cholesterol (LDL), and the complications of diabetes.<sup>2,3</sup>

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated the unequivocal benefit of intensive treatment of dyslipidaemia and hypertension in terms of reducing cardiovascular event rate and mortality rate.<sup>4</sup> If individuals who are more likely to develop diabetes complications can be identified early, both lifestyle advice and pharmacotherapy can be targeted appropriately. This could make a very significant difference to outcomes for individuals with type 2 diabetes.

Previous studies have identified genetic variants where one allele is associated with higher adiposity but a healthier metabolic profile and lower risk of type 2 diabetes, heart disease and hypertension in the general population.<sup>5–7</sup> These variants were named ‘favourable adiposity’ due to their paradoxical associations with adiposity and risk of disease. The ‘favourable adiposity’ variants confer a favourable metabolic profile even in those individuals with a higher body mass index (BMI).<sup>5</sup> MRI scans of abdominal fat distribution have revealed that people with more favourable alleles are able to store more of the extra fat subcutaneously leading to less ectopic liver fat which results in a

#### Whats’ New?

- Recently, ‘favourable adiposity’ genetic variants associated with higher adiposity but better metabolic profile have been identified in the general population.
- We show that a ‘favourable adiposity’ genetic score is associated with higher weight but a healthier lipid profile in people with type 2 diabetes, and lower odds of requiring lipid-lowering or anti-hypertensive medication during the course of their disease.
- In the future, stratifying people into those with and without favourable adiposity might potentially allow for both lifestyle management and pharmacotherapy to be targeted appropriately to reduce metabolic complications and co-morbidities.

favourable metabolic profile despite higher adiposity.<sup>5</sup> The role of ‘favourable adiposity’ genetic variants on glycaemic control and metabolic profile of people who already have type 2 diabetes is not clear.

In this study, we aimed to determine whether individuals with type 2 diabetes who have higher genetic predisposition to ‘favourable adiposity’ have a better glycaemic control, healthier lipid profile, lower blood pressure and lower risk of cardiovascular events over time. We generated a genetic score for ‘favourable adiposity’ and investigated its association with the above cardiometabolic outcomes both cross-sectionally and longitudinally.

## 2 | METHODS

### 2.1 | Study participants

We used two independent UK-based cohorts of people with type 2 diabetes: (i) The Salford Diabetes Cohort<sup>8</sup> and (ii) a subset of the UK Biobank study participants<sup>9</sup> who were identified as having type 2 diabetes.

The analysis reported falls within the remit of the UK Biobank Ethical permission (Project Number ‘9072’ & ‘9055’) and the Salford Cohort Ethics Approval (IRAS ethics committee reference number: 128954).

#### 2.1.1 | UK Biobank

More than 500,000 individuals aged 37–73 years were recruited between 2006 and 2010 from across the UK as described in detail elsewhere.<sup>9</sup> We identified 12,787 European type 2 diabetes cases in the UK Biobank using collated general practitioner (GP) records as those not coded as having non-type 2 (e.g. monogenic, gestational) types of diabetes and either (a) any two of the following criteria were met: (1) quality and outcome framework (QOF) diagnosis codes for diabetes provided by the NHS in GP record data, (2)  $\text{HbA}_{1c} \geq 48$  mmol/mol (6.5%) and (3) a prescription for glucose-lowering medication, or (b) prescriptions were given for two or more different classes of glucose-lowering medication. We further restricted this to those with at least a 1-year gap from diagnosis without requiring insulin ( $n = 422$  were excluded) and age at diagnosis  $>35$  years (suggested by the Royal College of General Practitioners in their review for classification of diabetes in England<sup>10</sup>; ( $n = 487$  were excluded)), to limit the numbers of individuals with slow-progressing autoimmune diabetes or monogenic forms. This resulted in 11,914 individuals with type 2 diabetes who also had genetic data. Age of diagnosis was set as the lowest age recorded in GP records, hospital episode statistics (HES) records and self-reported at the interview, altering the GP-recorded age of diagnosis for 338 individuals.

Details of change in weight, BMI,  $\text{HbA}_{1c}$ , lipids and blood pressure for 15 time points with 1-year intervals were obtained from the GP records, where available, using only the measurements taken after diagnosis of diabetes. Records of events and prescriptions for medications including glucose-lowering medication, lipid-lowering medication, antihypertensive medication, myocardial infarction and stroke after the diagnosis of diabetes were taken from the UK Biobank assessment centre and collated GP records, as well as HES records for myocardial infarction and stroke. Date of first event for myocardial infarction and stroke post-diabetes diagnosis were recorded.

The codes, and their descriptions, used to extract these measures from the UK Biobank are provided in the supplementary method.

#### 2.1.2 | Salford diabetes Cohort

The Salford prospective diabetes study is a cohort of individuals (94% Europeans) aged 37–88 years, nearly all with type 2 diabetes, established in 2002 and described in more details elsewhere.<sup>8</sup> Individuals were recruited consecutively from outpatient clinics and GP surgeries. We excluded individuals who have had bariatric surgery ( $n = 6$ ), were diagnosed with type 2 diabetes aged under 36 ( $n = 143$ ), had no recorded age of diagnosis ( $n = 28$ ), were aged under 36 at baseline ( $n = 45$ ) and individuals with one-off unusual weight readings ( $n = 3$ ).

Details of change in weight, BMI,  $\text{HbA}_{1c}$ , lipids and blood pressure for 15 time points with 1-year intervals were obtained from collated GP electronic health records, using individual patient identifiers. We included data on glucose-lowering medications, lipid-lowering medications, antihypertensive medications, myocardial infarction and stroke post-diabetes diagnosis.

### 2.2 | ‘Favourable adiposity’ genetic score

For the UK Biobank cohort, genotyping quality control was conducted by the UK Biobank itself.<sup>11</sup> We used the index bgen program to extract SNP dosages.<sup>12</sup> In the Salford study, we extracted DNA from 844 individuals from blood using the phenol/chloroform technique.<sup>13</sup> Extracted samples were sent to LGC (<https://www.biosearchtech.com>) for genotyping using KASP assays. We excluded variants if the call rate  $<95\%$  and the Hardy–Weinberg disequilibrium  $p < 0.01$ .

We constructed the genetic score for favourable adiposity by calculating the number of favourable adiposity alleles carried by each individual (unweighted) across 14 genetic variants previously identified by Ji et al. (2019) (Table S1).<sup>5</sup> We used an unweighted genetic risk score as employed and recommended by Ji et al. (2019)<sup>5</sup> and also because we did not want to add the additional layer of complexity of effect size, in what was essentially an exploratory study.

### 2.3 | Statistical analysis

We studied the association between the ‘favourable adiposity’ genetic score and the traits of interest cross-sectionally, using data from time point zero, and longitudinally, using data from all 15 time points. We corrected LDL and total cholesterol for lipid-lowering medication. We defined the

corrected measures as measured LDL/0.7 and total cholesterol/0.8 for those on lipid medication.<sup>14</sup> For any trait of interest, any unresolvable outliers were identified and excluded prior to the analysis.

Linear regression models were used to evaluate the association between the ‘favourable adiposity’ genetic score and the continuous outcomes, and logistic regression models were used for binary events.

In all the analyses, we used age in years at baseline, sex, genotyping platform and the first four ancestry principal components, where available, as covariates in the model. For the logistic regression models against myocardial infarction and stroke, we also adjusted for lipid and glucose-lowering medication and anti-hypertensive treatment. For the longitudinal analyses, we additionally corrected for years from the start of the study.

Myocardial infarction and stroke were defined as binary events by their occurrence. Subsequent death from either event or other causes was not included in the analysis. Missing data, including event status (resulting from loss of follow-up or dropout), were not imputed. Medication use was defined as a prescription issued after diabetes diagnosis. Medication adjusted for in logistic models and lipid medication used in cholesterol corrections was defined as a prescription issued within 6 months before the event and the start of the study, respectively, in the UK Biobank (using the codes given in the supplementary method) as this time interval suggests medication use at the time of interest. In the case of no event, the time of the last recorded GP visit or interview was imputed as the time of the event. In the Salford cohort, medication use was defined as medication reported at the start of the study.

For longitudinal analyses, we tested an interaction between the genetic score and change in repeated measures over time. We used mixed-effects regression models that incorporated the year of measurement. In the UK Biobank, where measures at different time points were available with differing intervals, we corrected the statistical models for the exact age at the measurements to be consistent with the Salford study. The linear mixed-effects model for the Salford cohort is given by:

$$\text{trait}_{ij} = \beta_0 + \beta_1 \text{year}_j + \beta_2 \text{age}_i + \beta_3 \text{genetic score}_i + \beta_4 \text{sex}_i + \beta_5 (\text{year}_j \times \text{genetic score}_i) + \varepsilon_i \quad (1)$$

where  $i = 1, \dots, 723$  are the individuals,  $j = 0, \dots, 15$  are the repeated measures and  $\varepsilon_i$  is the random error. The interaction term  $\beta_5$  is our parameter of interest in the longitudinal analyses to test whether an increase/decrease in any trait over time is associated with the genetic score. All statistical analyses were conducted using R software.<sup>9</sup>

To group individuals into high and low genetic score for ‘favourable adiposity’, we calculated the median of the genetic score in the whole UK Biobank to be 12. We then

grouped the individuals in each cohort into those (i) with a higher genetic score ( $\geq 12$  alleles) and (ii) a lower score ( $< 12$  alleles) (Figure S1), and compared these two groups in terms of their average outcomes over integer time points (rounding GP record time points down to the nearest year for the UK Biobank). We compared these groups using a paired  $t$ -test to test the null hypothesis that the mean readings for each time point are equal across the two groups.

We conducted random-effects inverse variance-weighted meta-analysis for each of the above analyses to combine the results of both the Salford and the UK Biobank cohorts. We performed gender-stratified analyses to investigate the effect of sex.

### 3 | RESULTS

The mean and standard deviation of all the measures for both cohorts are given in Tables S2 and S3. There was a difference in age and time of measurements between the two cohorts, likely due to the narrower UK Biobank age range and the increased likelihood of dropout in GP records compared to the Salford study (Table S4). The median ‘favourable adiposity’ genetic score was 11 for both cohorts.

For the UK Biobank cohort, the counts of events and prescriptions were as follows: glucose-lowering medication (9644 treated and 2269 diet-only treatment), lipid-lowering medication (10,622 treated and 1291 not on lipid-lowering medication), antihypertensive medication (9351 treated and 2562 not on antihypertensive medication), myocardial infarction (1219 events and 10,523 no events) and stroke (1013 events and 10,770 no events). For the Salford cohort, the counts of events and prescriptions were as follows: glucose-lowering medication (586 treated and 137 diet-only treatment), lipid-lowering medication (639 treated and 84 not on lipid-lowering medication), antihypertensive medication (638 treated and 85 not on antihypertensive medication), myocardial infarction (133 events and 545 no events) and stroke (82 events and 614 no events).

Our linear regression models passed the diagnostic checks (Figure S2), with some deviation in the UK Biobank Q–Q plot that can be overlooked due to the Central Limit Theorem. The parameter estimates of the cross-sectional model and Equation 1 for the two cohorts are given in Tables S5 and S6 respectively.

A one standard deviation (SD) higher ‘favourable adiposity’ genetic score was associated with a 910 g higher weight ( $p = 2 \times 10^{-8}$ ) and 0.30 kg/m<sup>2</sup> higher BMI ( $p = 4 \times 10^{-8}$ ) but a favourable metabolic profile, including higher HDL ( $p = 8 \times 10^{-10}$ ) and lower triglycerides ( $p = 2 \times 10^{-5}$ ), as well as lower systolic blood pressure ( $p = .02$ ), in the UK Biobank study. However, these associations were not apparent in the meta-analysis with the smaller Salford study (Table 1). The

**TABLE 1** Cross-sectional association between ‘favourable adiposity’ genetic score and weight and metabolic profile of individuals with type 2 diabetes, using baseline measurements

Outcome	UK Biobank GP record				Salford				Meta-analysis		
	Beta	95% CI	P	N	Beta	95% CI	P	N	Beta	95% CI	P
Weight (kg)	.91	(0.59,1.23)	$2 \times 10^{-8}$	11,498	-.32	(-1.81,1.17)	.67	421	.52	(-0.61,1.65)	.37
BMI (kg/m <sup>2</sup> )	.30	(0.19,0.40)	$4 \times 10^{-8}$	11,492	-.06	(-0.57,0.45)	.81	409	.21	(-0.09,0.51)	.17
HbA <sub>1c</sub> (mmol/mol)	.21	(-0.09,0.51)	.18	11,638	2.01	(0.49,3.53)	.01	425	.95	(-0.79,2.69)	.29
HbA <sub>1c</sub> (%)	.02	(-0.01,0.05)	.18	11,638	.18	(0.05,0.32)	.01	425	.09	(-0.07,0.25)	.29
HDL (mmol/L)	.02	(0.01,0.02)	$8 \times 10^{-10}$	11,224	-.01	(-0.04,0.03)	.69	370	.01	(-0.01,0.03)	.29
Triglycerides (mmol/L)	-.04	(-0.07,-0.02)	$2 \times 10^{-5}$	10,910	.04	(-0.07,0.15)	.45	369	-.02	(-0.10,0.06)	.65
Total cholesterol* (mmol/L)	.00	(-0.02,0.02)	.97	11,495	-.03	(-0.14,0.08)	.57	411	.00	(-0.02,0.02)	.88
LDL* (mmol/L)	-.02	(-0.04,0.00)	.08	8,533	-.01	(-0.13,0.12)	.92	357	-.02	(-0.04,0.00)	.08
Systolic blood pressure (mmHg)	-.41	(-0.77, -0.06)	.02	11,576	1.52	(-0.11,3.14)	.07	434	.38	(-1.48,2.25)	.69
Diastolic blood pressure (mmHg)	.10	(-0.13,0.34)	.39	11,576	.41	(-0.61,1.42)	.43	434	.12	(-0.11,0.35)	.31

Beta is the change in trait per one SD (standard deviation) higher ‘favourable adiposity’ genetic score.

Abbreviations: 95% CI: 95% confidence interval; BMI: body mass index, HbA<sub>1c</sub>: glycated haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

\*Total cholesterol and LDL are corrected for lipid medication; N: number of samples; P: *p* value.

lack of association in the Salford study is likely the result of the significant difference in age and other participant characteristics between the two cohorts and more importantly, the application of intense weight management programmes in the Salford study. We did not detect any cross-sectional association with HbA<sub>1c</sub>, total cholesterol, LDL and diastolic blood pressure and no sex-specific association (Table S7).

In the UK Biobank cohort, after capping the length of follow-up at 15 years, the mean duration of follow-up was  $8.0 \pm 5.4$  years. Overall mean decrease in weight was 2.6 kg (95% confidence interval [CI] 2.8, 2.5). However, 32% of individuals increased their weight over the follow-up period. There was a detectable decrease in HbA<sub>1c</sub> at 2.90 mmol/mol [3.23, 2.57] (0.27% [0.30, 0.23]); 43% of individuals increased their HbA<sub>1c</sub> over the repeat measures. HDL increased over time by 0.03 mmol/L [0.03, 0.04], with 36% showing a drop; while both triglycerides and LDL showed decreases of 0.23 mmol/L [0.25, 0.21] and 0.41 mmol/L [0.43, 0.39], respectively, with 35% and 25% showing rises in these traits. There was an increase in LDL levels in the last few visits (Figure 1), which could be the result of a drop in the sample size (Table S2). Mean decrease in systolic blood pressure was 5.9 mmHg [6.2, 5.5], with 34% of people showing an increase over time.

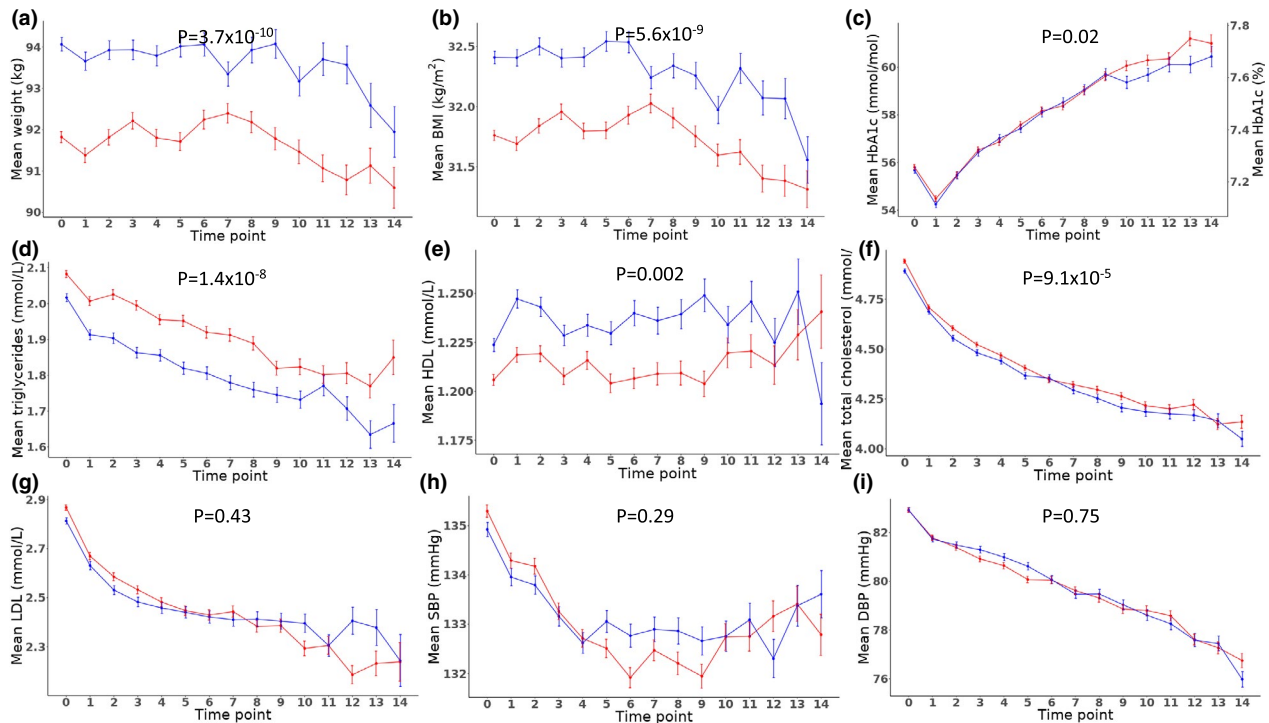
In the Salford cohort, the mean duration of follow-up was  $11.5 \pm 2.4$  years. Overall mean decrease in weight was 4 kg [5, 3]; however, 36% of individuals increased their weight over the follow-up period. There was also a decrease in HbA<sub>1c</sub> at 3.97 mmol/mol [5.58, 2.35] (0.36% [0.51, 0.22]) and 40%

of individuals increased their HbA<sub>1c</sub> over the repeat measures. Change in HDL was not significant at 0.01 mmol/L [-0.01, 0.04], with 49% of participants reducing their HDL over time. Triglycerides, LDL and systolic blood pressure all reduced over time by 0.44 mmol/L [0.52, 0.36], 0.67 mmol/L [0.75, 0.60], and 4.9 mmHg [6.7, 3.1], respectively, with 30%, 19% and 38% instead showing increases for each trait.

A higher ‘favourable adiposity’ genetic score was associated with a greater increase in BMI ( $p = .03$ ) over 15 years on average, in the meta-analysis of the UK Biobank and the Salford study. There was no evidence (at  $p < .05$ ) of interaction between the ‘favourable adiposity’ genetic score and change in weight, HbA<sub>1c</sub>, triglycerides, total cholesterol, HDL, LDL or blood pressure over the follow-up period (Table 2) or any sex-specific association (Table S8).

In the UK Biobank, those in the higher ‘favourable adiposity’ genetic score group had small, but consistent and statistically significant differences from the lower genetic score group (Figure 1). These included higher weight ( $p = 3.7 \times 10^{-10}$ ) and higher BMI ( $p = 5.6 \times 10^{-9}$ ) across multiple time points, but higher HDL ( $p = .002$ ), lower triglycerides ( $p = 1.4 \times 10^{-8}$ ), lower total cholesterol ( $p = 9.1 \times 10^{-5}$ ) and lower HbA<sub>1c</sub> ( $p = .02$ ). In Salford, we observed smaller differences with larger confidence intervals which may relate to the relatively small numbers of individuals in the higher genetic score group ( $n = 245$ ) and the application of intense weight management programmes in that area of the UK (Figure S1).

In the meta-analysis of the UK Biobank and Salford, we did not detect any association between the continuous



**FIGURE 1** The genetic effect of ‘favourable adiposity’ on change in (a) weight, (b) body mass index (BMI), (c) glycosylated haemoglobin (HbA<sub>1c</sub>), (d) triglycerides, (e) high-density lipoprotein (HDL), (f) total cholesterol, (g) low-density lipoprotein (LDL), (h) systolic blood pressure and (i) diastolic blood pressure from 15 follow-up time points with 1-year intervals from the UK Biobank. We grouped the cohort into (i) individuals who had 50% or more of the ‘favourable adiposity’ alleles (blue lines) and (ii) individuals who had less than 50% of the alleles (red lines). \*Total cholesterol and LDL are corrected for lipid medication. *p* values are from a paired *t*-test examining the null hypothesis that the means of the two groups are equal over time

‘favourable adiposity’ genetic score and risk of myocardial infarction or stroke. However, for those in a higher ‘favourable adiposity’ genetic score group, there was a trend towards a lower risk of myocardial infarction and/or stroke (odds ratio (OR) 0.79 [0.62, 1.00], *p* = .047) compared to the lower genetic score group, when using a binary genetic score group variable. A one SD higher genetic score was associated with lower odds of taking lipid-lowering medication (OR 0.91 [0.86, 0.97], *p* = .002) and anti-hypertensive medication (OR 0.95 [0.91, 0.99], *p* = .01) (Table 3).

## 4 | DISCUSSION

Our study suggests that having more ‘favourable adiposity’ alleles is associated with maintaining a marginally better lipid profile and blood pressure in spite of relatively higher adiposity in people with type 2 diabetes. This favourable effect lasts for several years after diagnosis.

The identification of ‘favourable adiposity’ genetic variants was originally carried out in population-based cohorts.<sup>5</sup> In a general population, these alleles are associated with higher adiposity, but a favourable cardiometabolic profile.

Our study extends this finding to people with type 2 diabetes by showing that even in those who already have type 2 diabetes, these alleles are associated with higher weight but higher HDL, lower triglycerides and lower systolic blood pressure.

Our longitudinal study revealed that those who have a higher ‘favourable adiposity’ genetic score do not change their weight over time on average, but they have constantly higher weight during their course of disease compared to those with a lower genetic score. Furthermore, the longitudinal results show that having a higher genetic score does not help with glycaemic control but it helps with maintaining a relatively good lipid profile by having higher HDL, lower triglycerides and lower cholesterol. However, while the general associations with the ‘favourable adiposity’ alleles were confirmed in the UK Biobank, they are very weak in terms of the changes in lipids, and as such are unlikely to be useful for clinical decision-making at the present time.

We have shown that having a higher ‘favourable adiposity’ genetic score is associated with lower odds of taking lipid-lowering or anti-hypertensive medication after diabetes diagnosis, and that for those who have a higher ‘favourable adiposity’ genetic score ( $\geq 12$  alleles) there is a

TABLE 2 Association between 'favourable adiposity' genetic score and change in weight and metabolic profile of individuals with type 2 diabetes over a time period of 15 years on average

Component	UK Biobank GP record						Salford						Meta-analysis					
	Beta	95% CI	P	N	Obs	FU	Beta	95% CI	P	N	Obs	FU	Beta	95% CI	P			
Weight (kg)	.0061	(-0.0035,0.0157)	.21	11,507	15.2	7.2	-.0028	(-0.0463,0.0407)	.9	476	13.8	11.2	.0057	(-0.0037,0.0151)	.23			
BMI (kg/m <sup>2</sup> )	.004	(0.0005,0.0075)	.02	11,507	15.4	7.2	.0013	(-0.0146,0.0172)	.87	476	13.8	11.0	.0039	(0.0004,0.0073)	.03			
HbA <sub>1c</sub> (mmol/mol)	-.0128	(-0.0265,0.0009)	.07	11,647	15.7	7.2	.0073	(-0.0513,0.0659)	.81	476	13.8	11.1	-.0118	(-0.0251,0.0016)	.08			
HbA <sub>1c</sub> (%)	-.0012	(-0.0024,0)	.07	11,647	15.7	7.2	.0007	(-0.0046,0.006)	.81	476	13.8	11.1	-.0011	(-0.0023,0)	.06			
HDL (mmol/L)	.0002	(0.0,0.0004)	.08	11,233	9.2	6.3	.001	(-0.0002,0.0022)	.09	471	13.8	10.9	.0004	(-0.0003,0.001)	.25			
Triglycerides (mmol/L)	-.0005	(-0.0015,0.0005)	.32	10,919	9.3	6.3	-.0005	(-0.0048,0.0038)	.84	470	13.8	10.0	-.0005	(-0.0015,0.0005)	.31			
Total cholesterol* (mmol/L)	.0002	(-0.0008,0.0012)	.74	11,504	11.8	6.8	-.0001	(-0.0042,0.004)	.96	475	13.8	11.1	.0002	(-0.0008,0.0011)	.71			
LDL* (mmol/L)	.0011	(-0.0003,0.0025)	.11	8,542	7.3	5.3	.0004	(-0.0059,0.0067)	.89	469	13.8	9.7	.0011	(-0.0003,0.0024)	.12			
Systolic blood pressure (mmHg)	.0066	(-0.0059,0.0191)	.31	11,585	25.0	7.4	-.0423	(-0.1001,0.0155)	.15	476	13.8	11.3	-.0094	(-0.0543,0.0356)	.68			
Diastolic blood pressure (mmHg)	.0024	(-0.0054,0.0102)	.54	11,585	24.7	7.4	-.0255	(-0.06,0.009)	.15	476	13.8	11.3	-.0063	(-0.0316,0.019)	.63			

Beta, 95% CIs and *p* values are provided for the interaction term (genetic score × follow-up time point).

Abbreviations: 95% CI: 95% confidence interval; BMI: body mass index; FU: Mean length of follow-up (years); HbA<sub>1c</sub>: glycated haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein. \*Total cholesterol and LDL are corrected for lipid medication; *N*: number of samples; Obs: Mean number of observations; *P*: *p* value.



TABLE 3 The genetic effect of 'favourable adiposity' on medication use and risk of myocardial infarction and stroke

Model	Outcome	UK biobank GP record				Salford				Meta-analysis			
		Odds ratio	95% CI	P	N	Odds ratio	95% CI	P	N	Odds ratio	95% CI	P	
Genetic score	Myocardial Infarction	0.98	(0.91,1.06)	.61	11,243	1.09	(0.86,1.40)	.48	498	0.99	(0.92,1.07)	.79	
	Stroke	0.96	(0.89,1.03)	.27	11,605	1.06	(0.80,1.42)	.68	518	0.97	(0.90,1.04)	.33	
	Myocardial Infarction and/or Stroke	0.96	(0.91,1.01)	.08	11,864	1.00	(0.82,1.23)	.97	534	0.96	(0.92,1.01)	.09	
	Glucose-lowering medication	0.97	(0.93,1.02)	.24	11,904	0.96	(0.78,1.19)	.74	540	0.97	(0.93,1.02)	.23	
	Lipid-lowering medication	0.91	(0.86,0.97)	.002	11,904	0.93	(0.72,1.19)	.54	540	0.91	(0.86,0.97)	.002	
Higher genetic score vs. lower genetic score	Antihypertensive medication	0.95	(0.91,0.99)	.02	11,904	0.83	(0.64,1.08)	.17	540	0.95	(0.91,0.99)	.01	
	Myocardial Infarction	0.96	(0.65,1.41)	.84	11,243	0.93	(0.29,2.97)	.90	498	0.96	(0.66,1.38)	.82	
	Stroke	0.76	(0.53,1.09)	.14	11,605	0.88	(0.23,3.41)	.85	518	0.77	(0.55,1.09)	.14	
	Myocardial Infarction and/or Stroke	0.79	(0.62,1.01)	.06	11,864	0.72	(0.27,1.94)	.52	534	0.79	(0.62,1.00)	.047	
	Glucose-lowering medication	0.91	(0.72,1.14)	.40	11,913	0.69	(0.24,1.92)	.47	543	0.90	(0.72,1.12)	.33	
Lipid-lowering medication	Lipid-lowering medication	0.68	(0.51,0.91)	.01	11,913	0.66	(0.20,2.26)	.51	543	0.68	(0.52,0.90)	.007	
	Antihypertensive medication	0.82	(0.66,1.02)	.07	11,913	0.57	(0.16,2.07)	.39	543	0.81	(0.65,1.01)	.06	

Odds ratio is reported per one SD (standard deviation) higher 'favourable adiposity' genetic score; 95% CI: 95% confidence interval; P: p value; N: number of samples.

trend towards a reduced risk of myocardial infarction and/or stroke compared to those with a lower genetic score. Both of these may be the result of a beneficial lipid and blood-pressure profile prior to the diagnosis of diabetes and during the course of the disease. We do not have specific information on the drivers for statin prescribing. However, it may well be the case that as in the general population, the people who receive statin treatment are those with a greater cardiovascular risk and so these individuals will intrinsically have a higher cardiovascular event rate than those not prescribed statin therapy.<sup>15</sup> This could reflect that people with a higher genetic score are assessed to be at lower risk by the cardiovascular risk assessment undertaken in primary care. It has been previously reported that the likelihood of a statin being prescribed was not necessarily related to the lipid profile itself in people with diabetes.<sup>16</sup> Furthermore, if the 'favourable adiposity' genetic score is associated with increased case fatality from myocardial infarction, this estimate would be biased towards a larger effect size. A larger amount of prospective data will be needed to validate this finding.

Among many possible mechanisms, the local and systemic effect of ectopic fat is postulated to explain the higher risk of hypertension, dyslipidaemia, heart disease and stroke in people with type 2 diabetes.<sup>17–23</sup> The mechanism by which the 'favourable adiposity' genetic score is protecting against risk of disease is likely to be through its association with the ability to store excess fat more subcutaneously which subsequently prevents ectopic lipid accumulation.<sup>5</sup> This could explain why individuals who have a higher 'favourable adiposity' genetic score have lower blood pressure, and lower risk of myocardial infarction or stroke in spite of relatively higher adiposity.

Our study is unique as it is among few studies using genetic scores within people with diabetes. Previous studies consist of those which used genetic scores of type 1 diabetes to discriminate type 1 from type 2 or monogenic forms of disease<sup>24,25</sup> or to predict progression to insulin therapy in clinically diagnosed people with type 2 diabetes<sup>26</sup> or to delineate risk genotypes for type 2 diabetes.<sup>27,28</sup> Type 2 diabetes is a complex and common condition. Over time, as many as 45% of individuals develop dyslipidaemia and 35% develop high blood pressure but the proportions are highly dependent on the intensity of monitoring and of treatment and treatment concordance.<sup>4</sup> Identifying ways of stratifying cardiometabolic risk in people with type 2 diabetes could allow for both lifestyle management and pharmacotherapy to be targeted appropriately to reduce the metabolic complications and co-morbidities as time goes forward. Genetics of favourable adiposity may aid this process but further research is required to test its generalisability and predictive value alongside known cardiovascular genetic variants.

## 4.1 | Study strengths and limitations

The strength of our study is both a cross-sectional and long-term follow-up design with comprehensive metabolic characterisation that can be collected through primary care follow-up. We had follow-up data over 15 years for both the UK Biobank and Salford participants; two independently sampled groups. It is expected that as time goes on, more follow-up data will become available. However, the phenotypic follow-up data are subject to the inaccuracies of data collection in a real-world healthcare setting.

Our study is subject to some bias mainly due to the medication taken by our participating individuals. It is the case that those with a higher 'favourable adiposity' genetic score may more often result in being overweight or obese and if diabetes is diagnosed, these individuals may more often receive weight-lowering treatment, such as GLP-1 analogues. These treatments would counteract the further increase in weight that would have been observed with a weight-neutral treatment; while also in the case of a GLP-1 analogue would reduce cardiovascular risk. Furthermore, many treatments that have been utilised for type 2 diabetes in recent years have modulating effects on adipose tissue distribution. These medications are continually titrated to 'treat to target' in people with type 2 diabetes in the UK clinical setting. In other words, the sometimes frequent changes in medication, some of which such as sulphonylureas, thiazolidinediones (glitazones), sodium glucose-like transport-2 inhibitors (SGLT-2is), glucagon-like peptide-1 (GLP-1) agonists and insulin can have a profound effect on weight trajectory and blood glucose levels.<sup>29</sup>

The other bias which could have affected our results is collider bias (or index event bias).<sup>30</sup> A collider is a trait (here type 2 diabetes status) that is influenced by two other traits of interest (e.g. here genetics of 'favourable adiposity' and triglycerides), which can induce a false association or reverse the sign of true associations. In this study, we focused on individuals with type 2 diabetes. People with a higher 'favourable adiposity' genetic score in our study probably had worse insulin secretion or had other risk factors to develop diabetes in the first place. However, there is no evidence to suggest lower insulin secretion is associated with higher BMI and a favourable metabolic profile. Furthermore, there was no association between the 'favourable adiposity' genetic score and HbA<sub>1c</sub>. In fact, in the UK Biobank where we had more data on HbA<sub>1c</sub>, we detected a reverse association between the 'favourable adiposity' genetic score and HbA<sub>1c</sub>. Finally, the association between the 'favourable adiposity' genetic score and higher BMI and a favourable lipid profile was established in population-based cohorts.<sup>5</sup>

One further limitation of the UK Biobank GP records data is that loss of follow-up increases over time, as individuals are likely to make fewer visits to the GP as the time from

type 2 diabetes diagnosis increases, leading to much smaller sample sizes later on.

## 5 | CONCLUSION

We found that the genetics of ‘favourable adiposity’ is associated with higher weight but a more favourable lipid profile and lower blood pressure in people already diagnosed with type 2 diabetes in the UK Biobank and that this favourable effect is maintained over time. These observed effects are independent of glycaemic control. However, the magnitude of the effects are small and as such are unlikely to be useful for clinical decision-making at present. Future studies may determine whether a genetic predisposition to favourable adiposity in people with type 2 diabetes could improve the prognosis of the disease in terms of less cardiovascular events.

### AUTHOR CONTRIBUTION STATEMENT

AHH and HY conceived the study and wrote the first draft. SM conducted the data analysis. AHH, SM, HY, HDG, KGY, HF, NM, KS, GC, JT, RNB, RD, RPN, WO, TMF and MG contributed to the writing and provided an overview of the manuscript. All authors approved the final version. HY is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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### CONFLICT OF INTEREST

All authors declared no conflict of interest.

### ETHICS

The analysis reported falls within the remit of the UK Biobank Ethical permission (Project Number ‘9072’ & ‘9055’) and the Salford Cohort Ethics Approval.

### DATA AVAILABILITY STATEMENT

We used patient-level data which was fully anonymised prior to analysis. Any requests for access to the Salford data should be made to Dr Adrian Heald.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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