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# A Mendelian randomization study provides evidence that adiposity and dyslipidemia lead to lower urinary albumin creatinine ratio, a marker of microvascular function 

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[^0]A Mendelian randomization study provides evidence that adiposity and dyslipidemia lead to lower urinary albumin creatinine ratio, a marker of microvascular function<br>Francesco Casanova ${ }^{1}$, Andrew R. Wood², Hanieh Yaghootkar ${ }^{2,3}$, Robert N. Beaumont², Samuel E. Jones ${ }^{2}$, Kim M. Gooding ${ }^{1}$, Kunihiko Aizawa ${ }^{1}$, W. David Strain ${ }^{1}$, Andrew T. Hattersley ${ }^{1}$, Faisel Khan ${ }^{4}$, Angela C. Shore ${ }^{1}$, Timothy M. Frayling ${ }^{2}$ \& Jessica Tyrrell ${ }^{2}$

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#### Abstract

Urinary albumin-creatinine ratio is a marker of diabetic nephropathy and microvascular damage. Metabolic-related traits are observationally associated with ACR but their causal role is uncertain. Here, we confirmed ACR as a marker of microvascular damage and tested whether metabolic-related traits have causal relationships with ACR.

The association between ACR and microvascular function (responses to acetylcholine and sodium nitroprusside) were tested in the SUMMIT study. Two sample Mendelian randomization (MR) was used to infer the causal effects of eleven metabolic risk factors, including glycemic, lipid and adiposity traits on ACR. MR was performed in up to 440,000 UK Biobank and 54,451 CKDGen participants.

ACR was robustly associated with microvascular function measures in SUMMIT. Using MR we inferred that higher triglyceride and LDL-cholesterol levels caused elevated ACR. A one standard deviation (SD) higher triglyceride and LDL-C level caused a 0.062 [ $95 \% \mathrm{Cl}: 0.040$, 0.083 ] and a 0.026 [ $95 \% \mathrm{Cl}: 0.008,0.044$ ] SD higher ACR respectively. There was evidence that higher body fat and visceral body fat distribution caused elevated ACR, whilst a metabolically "favourable adiposity" phenotype lowered ACR.

ACR is a valid marker for microvascular function. MR suggested that 7 traits have causal effects on ACR, highlighting the role of adiposity related traits in causing lower microvascular function.


## Introduction

The urinary albumin-creatinine ratio, a marker of diabetic nephropathy, is used as a proxy for damage to the systemic microcirculation (1) and predicts first myocardial infarction and mortality in those with diabetes, post stroke and the general population (2-4). There is evidence linking metabolic-related traits, including adiposity, dyslipidemia and insulin resistance with elevated ACR levels and microvascular damage ( $5 ; 6$ ). It is well accepted that tight glucose control in patients with type 2 diabetes (T2D) reduces the risk of microvascular retinal complications (7; 8) and there is evidence that adiposity per se is associated with increased ACR. For example, population studies suggest that microalbuminuria is associated with central adiposity (9) and results from The Framingham Heart Study show that visceral but not subcutaneous fat is associated with increased albuminuria (10). Not all evidence linking metabolic-related traits come from randomized control trials and, in absence of these, the next best evidence of causality comes from genetic studies using a technique known as Mendelian randomization (MR, Figure 1).

In MR, genetic variants that are strongly associated with the risk factor of interest are used to test its causal effect on an outcome (11). The MR approach exploits the natural experiment of genetic variants being randomly assigned at conception, which means they are less likely to be associated with confounding factors and should not suffer from reverse causality (12). MR studies investigating the role of metabolic traits in increasing microvascular damage, including ACR, infer causal relationships for higher blood pressure (13) but not for lipids (14), but the latter study was small, limited in power and focused only on people with diabetes.

Here, we utilised data from 743 participants in the SUrrogate markers for Micro- and Macrovascular hard endpoints for Innovative diabetes Tools (15) study to first confirm that ACR is a suitable proxy for early systemic microvascular damage, by testing its association with two validated measures of microvascular function - skin microvascular response to iontophoresis of vasodilators acetylcholine (endothelial dependent) and sodium nitroprusside (endothelial independent). Second, we tested the observational associations between ACR and 9 metabolic
risk factors in 438,075 participants in the UK Biobank. Finally, we used MR to test the effects of 11 metabolic risk factors on microvascular function using ACR as a proxy in the UK Biobank and summary results for 54,451 participants in the CKDgen GWAS results.

## Methods

## Populations studied

## UK Biobank

The UK Biobank study recruited over 500,000 individuals aged between 37 and 73 years between 2006 and 2010. The study collected detailed information from all participants, via questionnaires, interviews and measurements (16). Here we used 438,075 individuals of White European ancestry (defined through principal component-based analyses (17) with ACR available. We also defined a subset of 368,754 unrelated individuals of European ancestry. Related individuals were defined using a KING Kinship and an optimal list of unrelated individuals was generated to allow maximum numbers of individuals to be included. Ancestral principal components were then generated within these identified individuals for use in subsequent analyses.

## SUMMIT

Data for observational association and functional measures of microvascular function were collected in 743 individuals from two centres (Exeter and Dundee) participating in the vascular imaging cohort of the SUMMIT study. SUMMIT is a multicentre study aiming at identifying markers that predict the risks of developing diabetes related chronic micro- and macro-vascular complications (15; 18).

## Validation of ACR as a proxy for microvascular function

In SUMMIT, skin microvascular function in the forearm is measured using laser Doppler fluximetry. A laser Doppler imager (LDI, Moor Instruments MODEL LDI2) was used to measure perfusion before and after iontophoresis of endothelium dependent (acetylcholine, ACH) and
endothelium independent (sodium nitroprusside) vasodilatory stimuli. The full protocol of the techniques used are detailed elsewhere (18).

ACR was measured in SUMMIT from random spot urine collection (Exeter Pathology Services, Royal Devon and Exeter NHS Foundation Trust, and Dundee Pathology Services, Ninewells NHS trust), in accordance with the UK national quality assessment scheme. Analysis of albumin concentration was performed using immunoturbidimetric method a detection limit of $3.0 \mathrm{mg} / \mathrm{L}$ (Cobas system, Roche), creatinine was measured using the Jaffe methods. In order to maintain a consistent approach with UK Biobank analysis, values below detection limit were set at 2.9 $\mathrm{mg} / \mathrm{L}$ prior to the calculation of the ratio. The ACR variable was inverse normalised prior to analysis.

The relationship between the gold standard microvascular functional measures and ACR was explored using linear regression models, with age and sex included as covariates.

## Exposure and outcome measures in UK Biobank

We selected 11 metabolic markers which have previously been associated with ACR and have strong genetic instruments available in the form of multiple variants (Supplementary table 2) identified in large genome wide association studies (GWAS). More information on how the outcome and exposures were defined in the UK Biobank are explained below.

OUTCOME: Albumin to creatinine ratio (ACR)

A continuous measure of ACR was derived using urinary measures of albumin and creatinine. If albumin was $<6.7 \mathrm{mg} / \mathrm{L}$ (the detection level of the assay in UK Biobank, http://biobank.ctsu.ox.ac.uk/crystal/docs/urine_assay.pdf) then the albumin was set at $6.7 \mathrm{mg} / \mathrm{L}$ prior to the calculation of the ratio, an approach consistent with that of previous studies (13; 19). Albumin was measured using immuno-turbidimetric analysis method (Randox Bioscience, UK) while creatinine was measured using enzymatic analysis method (Beckman Coulter, UK). The ACR variable was inverse normalised prior to analysis.

## EXPOSURES:

Nine of the eleven metabolic markers were measured in the UK Biobank.

## Lipids

Serum concentrations of LDL-Cholesterol (LDL-C, N=417,386) were obtained using an Enzymatic Selective Protection analysis method (Beckman Coulter AU5800, Beckman Coulter (UK), Ltd), HDL-Cholesterol (HDL-C, N=382,598) using a Enzymelmmuno-inhibition analysis method (Beckman Coulter AU5800, Beckman Coulter (UK), Ltd) and triglycerides (TG, N=417,825) using Enzymatic analysis method (Beckman Coulter AU5800, Beckman Coulter (UK), Ltd). More details on the acquisition of these biomarkers can be found here:
http://biobank.ndph.ox.ac.uk/showcase/docs/serum biochemistry.pdf

Body composition

We used three measures of body composition: body mass index (BMI), waist hip ratio (WHR) adjusted for BMI and, using genetics, a measure of higher body fat percentage but lower metabolic disease risk, termed favourable adiposity. BMI was calculated for all participants from measured weight and height $\left((\mathrm{kg}) / \mathrm{height}(\mathrm{m})^{2}\right)$ and was available for 436,631 individuals with ACR and genetic data available. WHR was calculated from measured waist and hip circumference measures and adjusted for BMI, this was available in 436,530 individuals. Body fat percentage was calculated from bioelectrical impedance data collected using Tanita BC418MA body composition analyser and was available in 430,546 individuals.

## Blood pressure

Systolic blood pressure (SBP, $\mathrm{N}=437,121$ ) and diastolic blood pressure (DBP, $\mathrm{N}=436,394$ ) were measured. The blood pressure readings were obtained from averaging two readings obtained in a seated position 5 minutes apart using an automated blood pressure device (Omron 705 IT , Omron Healthcare Europe B.V. Hoofddorp, The Netherlands). In participants where only one
valid blood pressure was available this was utilised. Blood pressure medication use was accounted for by adding 10 and 15 to diastolic and systolic measures respectively.

Type 2 diabetes (T2D)

Type 2 diabetes cases were defined through self-report of diabetes using the baseline questionnaire. Cases were participants diagnosed at $>35$ years of age, and without reporting of insulin use within the first year of diagnosis (20). This resulted in 13,799 cases and 415,908 controls (Table 1).

## Metabolic predictors not available in the UK Biobank

Two measures of glycemic control were not measured in the UK Biobank at the time of study: fasting glucose (FG) and fasting insulin (FI).

For all continuous measurements in UK Biobank values more than 4.56SD away from the mean were excluded. These variables when then inverse normalised prior to analysis.

The observational associations between the measured exposures and ACR were tested in UK Biobank using linear regression models, adjusted for age, sex and assessment centre.

## Genetic variants

For Mendelian randomization (MR) independent genetic variants were selected from the UK Biobank imputation dataset. Variants were excluded if imputation quality (INFO) was $<0.3$ or the minor allele frequency (MAF) was $<0.1 \%$.

The genetic variants for the exposure traits were selected based on published GWAS studies. Genetic variants were selected and extracted for the 11 metabolic markers including lipid levels (triglycerides, HDL-C and LDL-C), BMI, favourable adiposity (genetic variants associated with
higher body fat percentage but lower risk of metabolic disease (e.g. type 2 diabetes, coronary heart disease)), WHR (adjusted for BMI), systolic and diastolic blood pressure, type 2 diabetes, fasting glucose and fasting insulin (Supplementary table 2). Four variants were identified that were previously identified to associate with ACR at genome wide significance: rs1047891 (HDL variant), rs4865796 (fasting insulin variant), rs109953111 (DBP variant) and rs2068888 (triglyceride variant) (21).

The extracted genetic variants were utilised to create genetic risk scores (GRS) for each metabolic trait of interest. The variants were weighted by their effect size ( $\beta$-coefficient) obtained from the primary GWAS, where possible using GWAS that did not include data from the UK Biobank (equation 1). The weighted score was then rescaled to reflect the number of trait raising alleles (equation 2).

$$
\text { Weighted score }=\beta_{1} \times S N P_{1}+\beta_{2} \times S N P_{2}+\ldots \beta_{n} \times S N P_{n}(\text { Equation 1) }
$$

Weighted genetic risk score $=\frac{\text { weighted score x number of SNPs }}{\text { sum of the } \beta \text { coefficients }}($ Equation 2)

## Mendelian randomization

We used MR to test for causal relationships between our 11 metabolic risk factors as exposures and ACR as an outcome. MR relies on several assumptions as outlined in Figure 1:

- the exposure GRS are robustly associated with the relevant measured exposure


## (Supplementary table 1);

- the exposure GRS are not associated, independently of their effects on the exposure, with confounding factors that bias conventional epidemiological associations.
- the exposure GRS is only associated with the outcome via its effect on the modifiable exposure.

In this study, we employed several methods of MR: one and two-sample MR. The primary analyses utilised data from 438,075 UK Biobank participants with measured ACR. We extracted the genetic variants for the 11 known metabolic traits (Supplementary table 2) from the BOLTLMM (22) GWAS of ACR, which was adjusted for baseline age, sex, study centre, and genotyping array ( $0=$ BiLEVE, $1=$ Axiom UK Biobank interim release, $2=$ Axiom UK Biobank final release). We also extracted association statistics for the same SNPs from the largest GWAS of ACR (54,451 participants from CDKGen consortium meta-analysis, Teumer et al. 2016) which did not include the UK Biobank.

## Two-sample MR

Our primary MR approach was to use the inverse variance weighted (IVW) estimator. The IVW method involves a weighted regression of the effect sizes of variant-outcome associations against the effect sizes of the variant-risk factor associations constraining the intercept to zero. The beta coefficient from the weighted regression represents the standard deviation change in the ACR per SD change in the outcome variable (with the exception of type 2 diabetes, where we present our findings as an SD change in ACR per two-fold higher genetic liability for type 2 diabetes). Several sensitivity analyses were performed to test whether the MR IVW estimates are biased by genetic variants that affect the outcome independently of the exposure of interest (i.e. horizontal pleiotropy). These methods were MR-Egger regression (23) and the weighted median (WM) estimator (24). MR-Egger is similar to IVW, except that the intercept is unconstrained. The intercept in MR-Egger reflects the average pleiotropic effect across genetic variants. Hence this method is less susceptible to potentially pleiotropic variants having a stronger effect on the outcome compared with their effect on the primary traits. The weighted median method is also more resistant to pleiotropy and gives consistent estimates even when $50 \%$ of the variants are invalid. Given these different assumptions, if all methods are broadly consistent it strengthens our causal inference. The R code for the various 2-sample methods is available in (23; 24).

We performed sensitivity analyses for the four traits where one variant was known to be associated with ACR at genome-wide significance. Here, the 2-sample MR was repeated excluding that one variant.

The results from the 2-sample MR in the UK Biobank and the GWAS studies were metaanalysed using the metan command in Stata.

There is some overlap between the genetic variants for LDL-C, HDL-C and TG. Therefore, as well as individually exploring the role of the LDL-C, HDL-C and TG SNPs on the outcomes we also ran multivariate models adjusting for the other lipid associations (25). For example, when testing the causal role of LDL-C we included the LDL-C-SNP-TG association and the LDL-C-SNP-HDL association as covariates in our model.

## One sample MR

In an unrelated subset of the data we also performed one-sample MR using the GRS and the ivreg2 command in STATA. In these models age, sex, ancestral principal components, assessment centre and genotyping platform were included as covariates. In cases where the predictor was not measured in the UK Biobank we explored the association of the GRS directly with the outcome. As with the two sample MR we performed multivariate analyses for the lipids by adjusting models for the other lipid GRS. For example, we performed MR to explore the causal role of LDL-C on ACR adjusting our models for all the standard covariates and the HDLC and TG GRS.

Data and resource availability

The UK Biobank resource can be utilised by any bonafide researcher and access to all the genetic and phenotypic data utilised in this study are available upon application to the UK Biobank (https://www.ukbiobank.ac.uk/). The summary statistics from the CDKGEN are
available: (https://ckdgen.imbi.uni-freiburg.de). SUMMIT data utilised in this study are available on request to the Diabetes and Vascular Research Centre, University of Exeter Medical School.

## Results

Characteristics for the 438,075 UK Biobank and 743 SUMMIT participants are presented in table 1.

## SUMMIT provided evidence that supports the use of ACR as a marker of microvascular function

Results from the SUMMIT study support the use of ACR as a proxy for microvascular function with lower microvascular function associated with raised ACR levels. There was a negative association between ACR and skin microvascular function for both endothelium dependent (ACH) and independent (sodium nitroprusside) function. One SD lower response in endothelium dependent microvascular function as measured by skin reactivity to iontophoresis of ACH was associated with a 0.155 SD higher ACR ( $95 \% \mathrm{Cl}: 0.078,0.230, \mathrm{p}=5.8 \mathrm{E}-05$ ). One SD lower response in endothelium independent microvascular function as measured by reactivity to sodium nitroprusside was associated with a 0.206 SD higher ACR ( $95 \%$ CI: $0.131,0.281, \mathrm{p}=$ 1.1E-07). Taken together these measures demonstrate that lower systemic microvascular response measured by skin reactivity to iontophoresis is associated with elevation in urinary ACR.

## Observational associations for the 11 metabolic traits with ACR

Data for observational analyses in UK Biobank were available for 9 of the 11 of exposure traits. Observational analyses provided evidence that higher HDL cholesterol, systolic and diastolic blood pressure, higher WHR adjusted for BMI and type 2 diabetes were associated with elevated ACR (Table 2). Higher LDL cholesterol, triglycerides, BMI and higher body fat percentage were associated with lower levels of ACR (Table 2). The inverse association between higher LDL cholesterol, triglycerides, BMI and higher body fat with lower ACR was unexpected, but maybe due to treatment effects, confounding or survival bias, thus highlighting the importance of more robust approaches, like MR.

## Mendelian randomization finds a stronger causal role of triglycerides in elevating ACR compared to LDL-cholesterol

MR inferred a causal role of higher TG and LDL-C in elevating ACR, with the effect of TG more than twice that of LDL-C. A one-SD higher TG (approximately $86 \mathrm{mg} / \mathrm{dl}$ ) was associated with a 0.062 SD [ $95 \% \mathrm{CI}: 0.040,0.083$ ] higher ACR (approximately $9.3 \mathrm{mg} / \mathrm{mmol}$, Table 3, Figure 2), whilst a one-SD higher LDL-C (approximately $37 \mathrm{mg} / \mathrm{dl}$ ) was associated with a $0.026[95 \% \mathrm{Cl}$ : $0.008,0.044]$ SD higher ACR. There was no evidence to infer that higher HDL-C altered ACR. The evidence for a causal role of higher TG in elevating ACR was strengthened using multivariate MR which adjusted for the association of the TG SNPs with HDL-C and LDL-C. A one SD higher TG (adjusted for LDL-C and HDL-C) associated with a 0.094 SD [95\%CI: 0.073 , 0.115 ] higher ACR (Figure 2, Supplementary table 3). In contrast, multivariate analyses attenuated the association between LDL-C and ACR, with a one SD higher LDL-C (adjusted for TG and HDL-C) associated with a 0.018 SD [ $95 \% \mathrm{CI}$ : 0.001, 0.035] higher ACR (Figure 2, Supplementary table 3). There was no evidence that higher HDL-C adjusted for LDL-C and TG altered ACR.

Results were generally consistent when the more pleiotropy robust methods were utilised (Table 3). The estimates from the two studies (UK Biobank and CKDGen) and the one sample

MR in UK Biobank were consistent, strengthening the causal inference between triglycerides and ACR (Supplementary table 4, Supplementary figure 1). Findings for HDL and triglycerides were the same when variants known to be associated with ACR were excluded.

## Mendelian randomization finds causal role of body composition measures in elevating ACR

We next tested three measurements of body size and composition - BMI, waist hip ratio (adjusted for BMI) and metabolically "favourable adiposity".

The MR analyses suggested that higher WHR caused elevated ACR levels, independently of BMI. A one-SD higher WHR adjusted for BMI was associated with a 0.040 SD higher ACR ([95\%CI: 0.020, 0.059]; Table 3, Figure 3).

MR using the "favourable adiposity" genetic variants (associated with higher body fat percentage but lower risk of metabolic diseases (26) showed that metabolically favourable higher adiposity was associated with lower ACR $(-0.157[95 \% \mathrm{Cl}:-0.256,-0.057], P=0.002$; Figure 3).

The MR results for higher BMI were not conclusive, although they were directionally consistent with the WHR results.

Results from alternative MR methods (Table 3) and the study specific results from the UK Biobank, CKDGen and the one-sample MR results were generally consistent (Figure 3, Supplementary table 4). However, there was weak evidence of heterogeneity for BMI ( $\mathrm{P}=$ 0.013 , I-squared $83.9 \%$ ) and favourable adiposity ( $\mathrm{P}=0.027$, I-squared $79.5 \%$ ).

## Meta-analysis of two sample Mendelian randomization infers a causal role of type 2 diabetes in elevating ACR

MR inferred that genetic liability to type 2 diabetes caused elevated ACR levels, with a two-fold higher genetic liability to type 2 diabetes associated with 0.013 SD [95\%CI: $0.007,0.018$ ] higher ACR levels (Table 3, Figure 4). There was no evidence of a causal relationship between either fasting insulin or fasting glucose and ACR.

Results were consistent when alternative MR methods were used (Table 3, Supplementary table 4) and when excluding the fasting insulin SNP that is also associated with ACR. The study specific results from the UK Biobank and CKDGen are presented in Supplementary table 4, Figure 4.

## Mendelian randomization confirms causal role of blood pressure in elevating ACR

MR confirmed previous evidence (13) for the causal relationship between higher blood pressure and elevated ACR levels. A 1 mmHg higher systolic and diastolic blood pressure was causally associated with a 0.006 [ $95 \% \mathrm{Cl}: 0.004,0.008$ ] and 0.009 [ $95 \% \mathrm{Cl}: 0.006,0.012$ ] SD higher ACR respectively (Table 3, Figure 5).

Results were consistent when alternative MR methods were used, although not all reached $\mathrm{p}<0.05$ (Table 3). Excluding the one diastolic blood pressure variant that was associated with ACR in an independent study did not alter our findings. Study specific results from the UK Biobank, CKDGen and the one sample MR methods in the UK Biobank were generally consistent (Figure 5, Supplementary table 4), although there was evidence of heterogeneity for systolic blood pressure ( $P=0.002$, l-squared $89.6 \%$ ).

## Discussion

This study used genetic approaches to infer the causal role of 11 metabolic risk factors on ACR, which was considered as a proxy for microvascular dysfunction. Firstly, we confirmed that ACR is a valid proxy for microvascular function, using two gold standard physiological measures of microvascular function in the SUMMIT study - skin endothelial dependent and independent
microvascular function. We then used genetic variants as unconfounded proxies for the 11 metabolic risk factors to infer that 7 of the 11 metabolic risk factors cause elevated levels of ACR and thus cause microvascular dysfunction.

Skin microcirculation is an established model to investigate systemic microvascular function prior to the clinical manifestation of disease (27). Skin microvascular responses have been demonstrated to be reduced in people with type 2 diabetes (18) and associated with coronary microvascular function (28). Results presented here support the use of ACR as a proxy for the systemic microcirculation and not just for renal microcirculation.

In keeping with the clinical data, we inferred a causal role of LDL cholesterol and triglycerides in raising ACR levels, with multivariate lipid analyses strengthening the triglyceride association and attenuating the LDL association. Indeed, the effect of triglycerides on ACR is twice as large as the effect of LDL. This contrasts with available evidence for coronary artery disease (CAD) where LDL levels have a larger effect on CAD risk than triglycerides.

Whilst the effect sizes in our results can be seen as small, they represent clinically meaningful results. For example, previous studies have demonstrated that small changes in LDL cholesterol (e.g. 0.2 magnitude lower LDL in $\mathrm{mmol} / \mathrm{L}$ ) results in a 5 to $10 \%$ reduction in the risk of CHD (29). The majority of our analyses look at SD changes in ACR per genetically instrumented SD change in the predictor. For LDL, this equates to approximately a $0.9 \mathrm{mmol} / \mathrm{L}$ higher LDL, which in previous studies would equate to a 15 to $40 \%$ higher risk of CHD.

These results are consistent with those from clinical trials of cholesterol lowering medication. HMG Co-A reductase inhibitors (statins), predominantly lower LDL cholesterol, and have been demonstrated to reduce CAD risk. These drugs, however, only have a small effect on ACR (30), and a similarly small impact on other manifestations of microvascular dysfunction such as diabetic retinopathy (31). In contrast, PPAR $\alpha$ antagonists such as fenofibrate, which act predominantly on triglyceride levels, have been shown to have beneficial effect on diabetic nephropathy and retinopathy (32). Combined statin-fenofibrate therapies can provide additional
endothelial vascular benefits than statin and fenofibrate alone (33) and, according to the recent results of the ACCORD study, it appears to be safe with regards to the risk of myositis or rhabdomyolysis when used in combination with a statin (34). Our results suggest that combined therapies lowering triglyceride as well as LDL levels could provide compound benefits by reducing the atherosclerotic burden, and thus CAD, whilst simultaneously reducing microvascular dysfunction which has a greater impact on the quality of life on patients (35). We used three complementary measures of body composition to test the role of adiposity and body fat distribution on the ACR. These three measures were BMI, waist hip ratio (adjusted for BMI) as a measure of central adiposity and "favourable adiposity" as a measure of higher fat mass "uncoupled" from its adverse metabolic effects (26). Our MR analyses infer that higher WHR (adjusted for BMI ) elevates ACR. In contrast, having more favourable adiposity alleles lowers ACR. The favourable adiposity variants are known to associate with higher subcutaneous fat, but lower liver fat and lower visceral-to-subcutaneous adipose tissue ratio (26). This provides further evidence that body fat distribution may be important in albuminuria and microvascular problems. Previous studies have suggested a role for body fat distribution and visceral fat in albuminuria, although to date, these studies have had low numbers of participants and have only used observational data so are subject to more biases than the genetic approach employed in this study $(10 ; 36 ; 37)$. A consistent trend was also noted for BMI, with higher BMI trending towards elevated ACR. These results suggest that adiposity and distribution of fat are important in elevating ACR and suggests a causal role for adiposity and fat distribution in microvascular dysfunction.

Our analyses strengthen previous work demonstrating that higher systolic and diastolic blood pressure cause albuminuria (13). Our results confirmed the direction and magnitude of the MR inferred causal role of systolic and diastolic blood pressure on ACR recently reported (13) and support evidence from clinical trials showing that anti-hypertensive treatments acting on the Renin-angiotensin system reduce ACR (38).

As expected, our MR results confirm that diabetes plays a major role in raising ACR levels. These results add genetic evidence to the large body of data from observational studies and clinical trials clearly showing the role of T2D in causing renal damage. There was no genetic evidence for fasting insulin or fasting glucose levels causing elevated ACR levels. This is in contrast with observational studies showing an association between fasting insulin or fasting glucose and ACR levels $(39 ; 40)$. This may indicate that these observational associations are driven by confounding factors.

The major strength of this study is the availability of data in the UK Biobank and a large independent GWAS sample for testing the causal relationships using 2-sample MR approaches. Another strength is the use of multiple rigorous MR methods to establish causality in this analysis. MR provides the next best evidence of causality after randomized control trials and allow causal inferences on large scale databases such as those used in study.

We acknowledge, however, some limitations. Firstly, Mendelian randomization studies are not immune from some of the issues that affect observational studies. For example, it is possible that biases such as survival bias could have affected the MR as well as observational studies. If, for example, a high ACR and high LDL-cholesterol level results in a high mortality rate due to microvascular disease (e.g. stroke), then genetic factors that raise LDL-Cholesterol level could be depleted from the study and associations between LDL-cholesterol raising alleles and ACR could be weakened. This type of bias has been pointed out before (41). Secondly, our analyses were restricted to individuals of Caucasian descent and the UK Biobank is restricted to participants born between 1938 and 1971, therefore the generalisability of our findings may be limited. Thirdly, although multivariate MR was utilised to explore the role of the three lipids on ACR, there remains the potential for some residual bias due to the pleiotropic associations of the lipid variants, although more pleiotropy resistant methods generally provided consistent results. Finally, some of our instrumental variables explain only a small percentage of the variability of the outcome variable and therefore we might be underpowered to detect causal association in some of the analysis.

In conclusion, we have utilised a genetic approach to show the causal role of 7 metabolic risk factors on ACR and provided evidence that dyslipidemia, adiposity and distribution of adipose tissue cause elevations in ACR and thus cause microvascular dysfunction.

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## Authors' contributions

F.C., T.M.F., J.T. designed the study. F.C., T.M.F., J.T. wrote the manuscript. A.C.S., W.D.S., A.T.H., edited the manuscript and helped interpret the data. F.C., J.T., A.R.W., S.E.J., R.B., H.Y., K.H.G., K. A., F.K. performed data processing, statistical analyses and interpretation. A.C.S., W.D.S, K.M.G, obtained funding for, designed and supervised the SUMMIT study.

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## Transparency statement

J.T as the manuscript's guarantor confirms that the manuscript is an honest, accurate, and transparent account of the study being reported and no important aspects of the study have been omitted.

## Conflict of Interest

The authors report no conflicts of interest.

Table 1. Participants' characteristics. Data are presented as mean ( $\pm$ standard deviation) and median [25th -75th percentile] where not otherwise stated.

|  | UK Biobank | SUMMIT |
| :--- | :---: | :---: |
| N | 438,075 | 743 |
| Age (yrs) | $57.27( \pm 8.02)$ | $66.16( \pm 8.82)$ |
| Sex [N males (\%)] | $237,181(54.14 \%)$ | $480(64.60 \%)$ |
| Height (cm) | $168.7( \pm 9.2)$ | $169.6( \pm 0.09)$ |
| BMI | $27.38( \pm 4.75)$ | $29.55( \pm 5.22)$ |
| ACR (mg/mml) | $1.10[0.69-1.85]$ | $0.70[0.45-1.4]$ |
| CAD [N (\%)] | $36,434(10.53 \%)$ | $223(30.01 \%)$ |
| T2D [N $(\%)]$ | $13,799(3.21 \%)$ | $400(53.84 \%)$ |
| Systolic BP $(\mathrm{mmHg})$ | $144.2( \pm 24.0)$ | $136.7(16.5)$ |
| Diastolic BP $(\mathrm{mmHg})$ | $86.3( \pm 13.5)$ | $76.9(8.71)$ |

$\mathrm{BMI}=$ body mass index, $\mathrm{ACR}=$ albumin creatinine ratio, CAD = coronary arterial disease, available in 346,080 participants, T2D = type 2 diabetes, $\mathrm{BP}=$ blood pressure.

Table 2. UK Biobank observational association results between investigated traits and ACR for observational data.

| Trait | UK Biobank Beta* | UK Biobank SE | UK Biobank P |
| :---: | :---: | :---: | :---: |
| Diastolic BP | 0.113 | 0.001 | $<1.0 \mathrm{E}-15$ |
| Systolic BP | 0.155 | 0.002 | $<1.0 \mathrm{E}-15$ |
| HDL cholesterol | 0.068 | 0.002 | $<1.0 \mathrm{E}-15$ |
| LDL cholesterol | -0.018 | 0.002 | $<1.0 \mathrm{E}-15$ |
| Triglycerides | -0.047 | 0.002 | $<1.0 \mathrm{E}-15$ |
| BMI | -0.106 | 0.001 | $<1.0 \mathrm{E}-15$ |
| \% Body fat | -0.116 | 0.002 | $<1.0 \mathrm{E}-15$ |
| Waist hip ratio (adjusted by BMI) | 0.008 | 0.002 | 4.30E-07 |
| Fasting glucose | Not available | Not available | Not available |
| Fasting insulin | Not available | Not available | Not available |
| T2D | 0.353 | 0.008 | $<1.0 \mathrm{E}-15$ |

*Beta represents the standard deviation change in ACR per unit standard deviation change in continuous traits or change based on case-control status for binary traits. SE = standard error. $\mathrm{BP}=$ blood pressure, $\mathrm{BMI}=$ body mass index, $\mathrm{T} 2 \mathrm{D}=$ type 2 diabetes, $\mathrm{BP}=$ blood pressure.

Table 3. ACR results of meta analysis of Mendelian randomization results in UK Biobank and CKDGen. Betas represent standard deviation change in ACR for standard deviation change in metabolic trait, 95\% confidence interval in brackets.

| Trait | Main MR analysis |  | Beta Egger | Pleiotropy robust methods |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Beta IVW | P IVW |  | P Egger | Beta WM | P WM | Beta PWM | P PWM |
| Diastolic BP | 0.009 (0.006, 0.012) | 2.0E-09 | $-0.001(-0.009,0.008)$ | 8.3E-01 | $0.009(0.006,0.012)$ | $6.8 \mathrm{E}-10$ | $0.008(0.004,0.011)$ | $1.0 \mathrm{E}-05$ |
| Systolic BP | 0.006 (0.004, 0.008) | $3.8 \mathrm{E}-08$ | $0.001(-0.005,0.007)$ | 7.6E-01 | 0.006 (0.004, 0.007) | 2.9E-09 | 0.005 (0.003, 0.008) | 1.8E-06 |
| HDL cholesterol | -0.012 (-0.029, 0.006) | $1.9 \mathrm{E}-01$ | 0.012 (-0.013, 0.036) | $3.5 \mathrm{E}-01$ | 0.014 (-0.002, 0.030) | 7.7E-01 | 0.014 (-0.009, 0.037) | $2.5 \mathrm{E}-01$ |
| LDL cholesterol | 0.026 (0.008, 0.044) | 5.0E-03 | 0.022 (-0.006, 0.049) | $1.2 \mathrm{E}-01$ | 0.030 (0.014, 0.047) | 2.6E-04 | 0.027 (0.009, 0.045) | $3.8 \mathrm{E}-03$ |
| Triglycerides | 0.062 (0.040, 0.083) | 1.3E-08 | 0.064 (0.033, 0.096) | 5.6E-05 | 0.050 (0.030, 0.070) | 7.8E-07 | 0.054 (0.026, 0.082) | 1.3E-04 |
| BMI | 0.024 (-0.002, 0.050) | 7.3E-02 | 0.088 (0.031, 0.144) | 2.3E-03 | 0.015 (-0.015, 0.045) | $3.2 \mathrm{E}-01$ | 0.033 (-0.002, 0.068) | 6.1E-02 |
| Favourable adiposity* | -0.157 (-0.256, -0.057) | $1.9 \mathrm{E}-03$ | $0.082(-0.017,0.334)$ | 5.2E-01 | -0.143 (-0.230, -0.560) | 1.3E-03 | -0.143 (-0.266, -0.021) | 2.1E-02 |
| Waist hip ratio (adjusted by BMI) | 0.040 (0.020, 0.059) | 6.3E-05 | 0.099 (0.051, 0.146) | $4.9 \mathrm{E}-05$ | 0.050 (0.027, 0.073) | 2.0E-05 | 0.032 (0.008, 0.056) | 8.0E-03 |
| Fasting glucose | -0.014 (-0.073, 0.044) | 6.3E-01 | $-0.039(-0.152,0.074)$ | 5.0E-01 | -0.017 (-0.062, 0.028) | 4.5E-01 | -0.016 (-0.064, 0.032) | 5.0E-01 |
| Fasting insulin | -0.018 (-0.215, 0.179) | 8.6E-01 | $-1.318(-2.409,-0.227)$ | $1.8 \mathrm{E}-02$ | -0.035 (-0.159, 0.089) | $5.8 \mathrm{E}-01$ | -0.032 (-0.170, 0.106) | 6.5E-01 |
| T2D liability | 0.013 (0.006, 0.021) | 5.2E-04 | 0.021 (0.006, 0.036) | 7.6E-03 | 0.021 (0.012, 0.031) | $1.4 \mathrm{E}-05$ | 0.023 (0.011, 0.034) | 1.1E-04 |

$\overline{\text { IVW }}$ = inverse variance weighted instrumental variable analysis, $\mathrm{WM}=$ weighted median analysis, $\mathrm{PWM}=$ penalised weighted median analysis.
$\mathrm{BP}=$ blood pressure, $\mathrm{BMI}=$ body mass index, T2D = type 2 diabetes.
*Favourable adiposity - represents higher adiposity but lower metabolic disease risk using genetic variants identified in Ji et al (26).

When removing SNPs associated with ACR at genome wide significance the results were consistent with the previous results [Diastolic BP: Beta IVW = 0.069 ( $-0.050,0.188$ ), p = 7.5E10; HDL cholesterol: Beta IVW $=0.069(-0.050,0.188), p=4.1 \mathrm{E}-02$; Triglycerides: Beta IVW = 0.057 (0.037, 0.077). p = 1.5E-08; Fasting Insulin: Beta IVW = 0.014 (-0.153, 0.181), p = 8.7E01]

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## Assumption 2

Genetic variants are not associated with confounders


## Assumption 3

Genetic variants influence risk of the outcome through the exposure, not through other pathways

Page 33 of 58
Diabetes


Standard deviation differences in ACR per standard deviation differences in genetically instrumented lipids measures

| Body Mass Index |  |  |
| :---: | :---: | :---: |
| UKB | - | 0.01 (-0.02, 0.04) |
| CDKGEN_GWAS | $\square$ | 0.09 (0.03, 0.15) |
| Subtotal | $N$ | 0.02 (-0.00, 0.05) |
| Favourable Adiposity |  |  |
| UKB | - | -0.07 (-0.19, 0.06) |
| CDKGEN_GWAS |  | -0.29 (-0.45, -0.14) |
| Subtotal |  | -0.16 (-0.26, -0.06) |
| WHR adjusted by BMI |  |  |
| UKB | $\rightarrow$ | 0.04 (0.01, 0.06) |
| CKDGEN_GWAS | $\square$ | 0.07 (0.01, 0.12) |
| Subtotal | $\bigcirc$ | 0.04 (0.02, 0.06) |
| 1 1 1 1 1 <br> -.5 -.4 -.3 -.2 -.1 | $\begin{array}{ll} 1 & 1 \\ 0 & .1 \end{array}$ |  |

Standard deviation differences in ACR per standard deviation differences in genetically instrumented adiposity measures.

For BMI and favourable adiposity there was evidence of heterogeneity ( $\mathrm{p}=0.013$, I-squared $83.9 \%$ and $p=0.027$, l-squared $79.5 \%$, respectively). No evidence of heterogeneity were found for WHR adjusted by $\mathrm{BMI}(\mathrm{p}=0.313$, l-square $1.8 \%)$.

Page 35 of 58
Fasting Glucose UKB CKDGEN_GWAS
Subtotal

Fasting Insulin UKB CKDGEN_GWAS

Subtotal

Type 2 Diabetes
UKB
CKDGEN_GWAS
Subtotal


Standard deviation differences in ACR per standard deviation differences in genetically instrumented glycemic measures.
There was evidence of heterogeneity for type 2 diabetes ( $p=0.004, \mathrm{l}$-squared $87.9 \%$ ). There was no evidence of heterogeneity for for fasting glucose ( $p=0.631$, 1 -squared $0.0 \%$ ) and fasting insulin ( $p=$ 0.496 , l-squared $0.0 \%$ ).


Standard deviation differences in ACR per standard deviation differences in genetically instrumented blood pressure.
There was no evidence of heterogeneity for diastolic blood pressure ( $p=0.074$, I-square $68.7 \%$ ). Some evidence of heterogeneity were found for systolic blood pressure ( $p=0.002$, I-square $89.6 \%$ ).

Supplementary table 1. Strength of association of genetic instruments with measured exposure exposures.

| Trait | \% variance | F-statistic | P |
| :--- | :---: | :---: | :---: |
| Diastolic BP | 2.17 | 9962 | $<1.0 \mathrm{E}-15$ |
| Systolic BP | 1.74 | 7966 | $<1.0 \mathrm{E}-15$ |
| HDL cholesterol | 6.4 | 26895 | $<1.0 \mathrm{E}-15$ |
| LDL cholesterol | 4.36 | 19550 | $<1.0 \mathrm{E}-15$ |
| Triglycerides | 4.91 | 22189 | $<1.0 \mathrm{E}-15$ |
| BMI | 1.6 | 7295 | $<1.0 \mathrm{E}-15$ |
| Favourable adiposity | 0.1 | 468 | $<1.0 \mathrm{E}-15$ |
| Waist hip ratio (adjusted by BMI) | 1.5 | 6837 | $<1.0 \mathrm{E}-15$ |
| Fasting glucose | Not available | Not available |  |
| Fasting insulin | Not available | Not available |  |
| T2D | 0.6 | 2504 | $<1.0 \mathrm{E}-15$ |

Supplementary table2. Genetic variants utilised in Mendelian randomization analyses. Gene location as reported by the original study (where available).

| Trait | Genetic variant | Trait raising allele | Trait lowering allele | Beta from the primary GWAS* | Primary GWAS* reference | Gene Location |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| BODY MASS INDEX | rs1000940 | G | A | 0.019 | Locke et al., 2014 | RABEP1 |
| BODY MASS INDEX | rs10132280 | C | A | 0.023 | Locke et al., 2014 | STXBP6 |
| BODY MASS INDEX | rs1016287 | T | C | 0.023 | Locke et al., 2014 | FLJ30838 |
| BODY MASS INDEX | rs10182181 | G | A | 0.031 | Locke et al., 2014 | ADCY3 |
| BODY MASS INDEX | rs10733682 | A | G | 0.017 | Locke et al., 2014 | LMX1B |
| BODY MASS INDEX | rs10938397 | G | A | 0.04 | Locke et al., 2014 | GNPDA2 |
| BODY MASS INDEX | rs10968576 | G | A | 0.025 | Locke et al., 2014 | LINGO2 |
| BODY MASS INDEX | rs11057405 | G | A | 0.031 | Locke et al., 2014 | CLIP1 |
| BODY MASS INDEX | rs11126666 | A | G | 0.021 | Locke et al., 2014 | KCNK3 |
| BODY MASS INDEX | rs11165643 | T | C | 0.022 | Locke et al., 2014 | PTBP2 |
| BODY MASS INDEX | rs11191560 | C | T | 0.031 | Locke et al., 2014 | NT5C2 |
| BODY MASS INDEX | rs11583200 | C | T | 0.018 | Locke et al., 2014 | ELAVL4 |
| BODY MASS INDEX | rs1167827 | G | A | 0.02 | Locke et al., 2014 | HIP1 |
| BODY MASS INDEX | rs11688816 | G | A | 0.017 | Locke et al., 2014 | EHBP1 |
| BODY MASS INDEX | rs11727676 | T | C | 0.036 | Locke et al., 2014 | HHIP |
| BODY MASS INDEX | rs11847697 | T | C | 0.049 | Locke et al., 2014 | PRKD1 |
| BODY MASS INDEX | rs12286929 | G | A | 0.022 | Locke et al., 2014 | CADM1 |
| BODY MASS INDEX | rs12401738 | A | G | 0.021 | Locke et al., 2014 | FUBP1 |
| BODY MASS INDEX | rs12429545 | A | G | 0.033 | Locke et al., 2014 | OLFM4 |
| BODY MASS INDEX | rs12446632 | G | A | 0.04 | Locke et al., 2014 | GPRC5B |
| BODY MASS INDEX | rs12566985 | G | A | 0.024 | Locke et al., 2014 | FPGT-TNNI3K |
| BODY MASS INDEX | rs12885454 | C | A | 0.021 | Locke et al., 2014 | PRKD1 |
| BODY MASS INDEX | rs12940622 | G | A | 0.018 | Locke et al., 2014 | RPTOR |
| BODY MASS INDEX | rs13021737 | G | A | 0.06 | Locke et al., 2014 | TMEM18 |
| BODY MASS INDEX | rs13078960 | G | T | 0.03 | Locke et al., 2014 | CADM2 |
| BODY MASS INDEX | rs13191362 | A | G | 0.028 | Locke et al., 2014 | PARK2 |
| BODY MASS INDEX | rs1516725 | C | T | 0.045 | Locke et al., 2014 | ETV5 |
| BODY MASS INDEX | rs1528435 | T | C | 0.018 | Locke et al., 2014 | UBE2E3 |
| BODY MASS INDEX | rs1558902 | A | T | 0.082 | Locke et al., 2014 | FTO |
| BODY MASS INDEX | rs16851483 | T | G | 0.048 | Locke et al., 2014 | RASA2 |
| BODY MASS INDEX | rs16951275 | T | C | 0.031 | Locke et al., 2014 | MAP2K5 |
| BODY MASS INDEX | rs17001654 | G | C | 0.031 | Locke et al., 2014 | SCARB2 |
| BODY MASS INDEX | rs17024393 | C | T | 0.066 | Locke et al., 2014 | GNAT2 |
| BODY MASS INDEX | rs17094222 | C | T | 0.025 | Locke et al., 2014 | HIF1AN |
| BODY MASS INDEX | rs17405819 | T | C | 0.022 | Locke et al., 2014 | HNF4G |
| BODY MASS INDEX | rs17724992 | A | G | 0.019 | Locke et al., 2014 | PGPEP1 |
| BODY MASS INDEX | rs1808579 | C | T | 0.017 | Locke et al., 2014 | C18orf8 |
| BODY MASS INDEX | rs1928295 | T | C | 0.019 | Locke et al., 2014 | TLR4 |

BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX BODY MASS INDEX DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE DIASTOLIC BLOOD PRESSURE

| rs2033529 | G | A | 0.019 |
| :---: | :---: | :---: | :---: |
| rs2033732 | C | T | 0.019 |
| rs205262 | G | A | 0.022 |
| rs2075650 | A | G | 0.026 |
| rs2112347 | T | G | 0.026 |
| rs2121279 | T | C | 0.025 |
| rs2176598 | T | C | 0.02 |
| rs2207139 | G | A | 0.045 |
| rs2245368 | C | T | 0.032 |
| rs2287019 | C | T | 0.036 |
| rs2365389 | C | T | 0.02 |
| rs2650492 | A | G | 0.021 |
| rs2820292 | C | A | 0.02 |
| rs29941 | G | A | 0.018 |
| rs3101336 | C | T | 0.033 |
| rs3736485 | A | G | 0.018 |
| rs3810291 | A | G | 0.028 |
| rs3817334 | T | C | 0.026 |
| rs3849570 | A | C | 0.019 |
| rs4256980 | G | C | 0.021 |
| rs4740619 | T | C | 0.018 |
| rs543874 | G | A | 0.048 |
| rs6477694 | C | T | 0.017 |
| rs6567160 | C | T | 0.056 |
| rs657452 | A | G | 0.023 |
| rs6804842 | G | A | 0.019 |
| rs7138803 | A | G | 0.032 |
| rs7141420 | T | C | 0.024 |
| rs7243357 | T | G | 0.022 |
| rs758747 | T | C | 0.023 |
| rs7599312 | G | A | 0.022 |
| rs7899106 | G | A | 0.04 |
| rs9400239 | C | T | 0.019 |
| rs9581854 | T | C | 0.03 |
| rs9925964 | A | G | 0.019 |
| rs10850411 | T | C | 0.253 |
| rs1173771 | G | A | 0.261 |
| rs13082711 | C | T | 0.238 |
| rs13139571 | C | A | 0.26 |
| rs1813353 | T | C | 0.415 |
| rs381815 | T | C | 0.348 |
| rs419076 | T | C | 0.241 |
| rs4373814 | C | G | 0.218 |
| rs4590817 | G | C | 0.419 |
| rs6015450 | G | A | 0.557 |
| rs10077885 | C | A | 0.17 |
| rs11128722 | G | A | 0.173 |
| rs11556924 | C | T | 0.21 |
| rs11953630 | C | T | 0.281 |
| rs12627651 | A | G | 0.204 |
| rs12940887 | T | C | 0.27 |
| rs12958173 | A | C | 0.179 |
| rs13107325 | C | T | 0.68 |
| rs1327235 | G | A | 0.308 |
| rs1361831 | C | T | 0.271 |
| rs1371182 | C | T | 0.252 |
| rs1450271 | T | C | 0.199 |
| rs1458038 | T | C | 0.457 |
| rs1620668 | G | A | 0.285 |
| rs17080093 | C | T | 0.411 |
| rs17638167 | C | T | 0.348 |
| rs1799945 | G | C | 0.457 |
| rs1975487 | G | A | 0.16 |

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TDRG1
RALYL
C6orf106
TOMM40
POC5
LRP1B
HSD17B12
TFAP2B
PMS2L11
QPCTL
FHIT
SBK1
NAV1
KCTD15
NEGR1
DMXL2
ZC3H4
MTCH2
GBE1
TRIM66
C9orf93
SEC16B
EPB41L4B
MC4R
AGBL4
RARB
BCDIN3D
NRXN3
GRP
NLRC3
ERBB4
GRID1
FOXO3
MTIF3
KAT8
TBX3
C5orf23, NPR3
SLC4A7
GUCY1A3, GUCY1B3
CACNB2
PLEKHA7
MECOM
CACNB2
C10orf107
EDN3, GNAS
TRIM36
FGD5
ZC3HC1
EBF1
CRYAA, SIK1
ZNF652
SETBP1
SLC39A8
JAG1
RSPO3
FIGN, GRB14
ADM
FGF5
ST7L, CAPZA1, MOV10
PLEKHG1
ELAVL3
HFE
PNPT1

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| rs2187668 | C | T | 0.372 |
| :---: | :---: | :---: | :---: |
| rs2291435 | C | T | 0.156 |
| rs2493134 | C | T | 0.275 |
| rs2521501 | T | A | 0.359 |
| rs2586886 | C | T | 0.254 |
| rs2891546 | G | A | 0.38 |
| rs2969070 | G | A | 0.182 |
| rs3184504 | T | C | 0.448 |
| rs3735533 | C | T | 0.445 |
| rs3752728 | A | G | 0.319 |
| rs4245739 | A | C | 0.243 |
| rs4247374 | C | T | 0.385 |
| rs592373 | A | G | 0.282 |
| rs6271 | C | T | 0.465 |
| rs633185 | C | G | 0.328 |
| rs6442101 | T | C | 0.303 |
| rs6891344 | A | G | 0.231 |
| rs7103648 | G | A | 0.241 |
| rs740746 | A | G | 0.32 |
| rs751984 | T | C | 0.376 |
| rs772178 | G | A | 0.208 |
| rs880315 | C | T | 0.257 |
| rs918466 | G | A | 0.182 |
| rs932764 | G | A | 0.224 |
| rs943037 | C | T | 0.482 |
| rs1060105 | C | T | 0.182 |
| rs10995311 | C | G | 0.21 |
| rs110419 | A | G | 0.159 |
| rs1126464 | C | G | 0.275 |
| rs12521868 | G | T | 0.191 |
| rs1378942 | C | A | 0.416 |
| rs16851397 | G | A | 0.375 |
| rs17249754 | G | A | 0.522 |
| rs17367504 | A | G | 0.547 |
| rs2304130 | G | A | 0.292 |
| rs2972146 | T | G | 0.172 |
| rs3774372 | C | T | 0.367 |
| rs6095241 | G | A | 0.168 |
| rs687621 | A | G | 0.188 |
| rs7302981 | A | G | 0.249 |
| rs805303 | G | A | 0.228 |
| rs8068318 | T | C | 0.262 |
| rs867186 | A | G | 0.265 |
| rs10078021 | G | T | 0.164 |
| rs1063281 | C | T | 0.2 |
| rs11030119 | G | A | 0.163 |
| rs12374077 | C | G | 0.163 |
| rs12405515 | G | T | 0.165 |
| rs12408022 | T | C | 0.198 |
| rs12906962 | C | T | 0.221 |
| rs12921187 | G | T | 0.174 |
| rs13205180 | T | C | 0.168 |
| rs143112823 | G | A | 0.403 |
| rs1438896 | T | C | 0.234 |
| rs2306374 | C | T | 0.184 |
| rs2760061 | A | T | 0.23 |
| rs2978098 | A | C | 0.165 |
| rs36022378 | C | T | 0.202 |
| rs4308 | A | G | 0.213 |
| rs4364717 | G | A | 0.175 |
| rs4952611 | C | T | 0.157 |
| rs55701159 | T | G | 0.285 |

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BAT2, BAT5
TBC1D1, FLJ13197
AGT
FURIN, FES
KCNK3
TBX5, TBX3
CHST12, LFNG
SH2B3
HOTTIP, EVX
PDE3A
MDM4
INSR
LSP1, TNNT3
DBH
FLJ32810, TMEM133
MAP4
CSNK1G3
RAPSN, PSMC3,
SLC39A13
ADRB1
LRRC10B
NCAPH
CASZ1
ADAMTS9
PLCE1
CYP17A1, NT5C2
SBNO1
ADO
LMO1
DPEP1
C5orf56
CYP1A1-ULK3
ZBTB38
ATP2B1
MTHFR, NPPB
ZNF101
Intergenic
ULK4
PREX1
ABO
CERS5
BAT2, BAT5
TBX2
PROCR
POC5
TNS1
BDNF
SENP2
DNM3
GPATCH2
chr15mb95
PPL
PKHD1
RP11-439C8.2
TEX41
SCAF4
WNT3A
SNX31
CAMKV, ACTBP13
ACE
MTAP
SLC8A1
ADCY3

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| rs6108168 | C | A | 0.211 |
| :---: | :---: | :---: | :---: |
| rs62012628 | C | T | 0.238 |
| rs62104477 | T | G | 0.177 |
| rs62524579 | G | A | 0.175 |
| rs6686889 | T | C | 0.185 |
| rs66887589 | C | T | 0.215 |
| rs67330701 | C | T | 0.367 |
| rs7178615 | G | A | 0.179 |
| rs72799341 | A | G | 0.185 |
| rs72812846 | T | A | 0.209 |
| rs743757 | C | G | 0.245 |
| rs745821 | T | G | 0.189 |
| rs7592578 | G | T | 0.24 |
| rs76326501 | A | C | 0.419 |
| rs79146658 | C | NA | 0.311 |
| rs8059962 | C | T | 0.17 |
| rs9372498 | A | T | 0.334 |
| rs953492 | A | G | 0.22 |
| rs9827472 | C | T | 0.177 |
| rs11715915 | C | T | 0.012 |
| rs7651090 | G | A | 0.013 |
| rs10747083 | A | G | 0.013 |
| rs340874 | C | T | 0.013 |
| rs9368222 | A | C | 0.014 |
| rs2302593 | C | G | 0.014 |
| rs6943153 | T | C | 0.015 |
| rs10814916 | C | A | 0.016 |
| rs6072275 | A | G | 0.016 |
| rs576674 | G | A | 0.017 |
| rs3783347 | G | T | 0.017 |
| rs3829109 | G | A | 0.017 |
| rs4869272 | T | C | 0.018 |
| rs11603334 | G | A | 0.019 |
| rs11619319 | G | A | 0.02 |
| rs174576 | C | A | 0.02 |
| rs11607883 | G | A | 0.021 |
| rs7903146 | T | C | 0.022 |
| rs4502156 | T | C | 0.022 |
| rs11708067 | A | G | 0.023 |
| rs11039182 | T | C | 0.023 |
| rs10811661 | T | C | 0.024 |
| rs983309 | T | G | 0.026 |
| rs1280 | T | C | 0.026 |
| rs780094 | C | T | 0.027 |
| rs11558471 | A | G | 0.029 |
| rs2191349 | T | G | 0.029 |
| rs11195502 | C | T | 0.032 |
| rs6113722 | G | A | 0.035 |
| rs16913693 | T | G | 0.043 |
| rs2908289 | A | G | 0.057 |
| rs560887 | C | T | 0.071 |
| rs10830963 | G | C | 0.078 |
| rs2972143 | G | A | 0.014 |
| rs2745353 | T | C | 0.014 |
| rs1530559 | A | G | 0.015 |
| rs731839 | G | A | 0.015 |
| rs4865796 | A | G | 0.015 |
| rs2820436 | C | A | 0.015 |
| rs1167800 | A | G | 0.016 |
| rs10195252 | T | C | 0.016 |
| rs9884482 | C | T | 0.017 |
| rs860598 | A | G | 0.018 |
| rs7903146 | C | T | 0.018 |

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PLCB1
ADAMTS7
CCNE1
RP11-273G15.2
chr1mb25
PDE5A
MYEOV
RP11-321F6.1
FBXL19
CPEB4
CACNA2D2
MAPK4
TMEM194B
AC016735.1
CCDC141
CMIP
SLC35F1
SDCCAG8
FAM208A
AMT
IGF2BP2
P2RX2
PROX1
CDKAL1
GIPR
GRB10

TOP1
KL
WARS
DNLZ
PCSK1
ARAP1
PDX1

CRY2
TCF7L2
VPS13C/C2CD4A/B
ADCY5
MADD
CDKN2B
PPP1R3B
SLC2A2
GCKR

DGKB/TMEM195
ADRA2A
FOXA2
IKBKAP

G6PC2
MTNR1B
IRS1
RSPO3
YSK4
PEPD
ARL15
LYPLAL1
HIP1
GRB14
TET2
TCF7L2

| FASTING INSULIN | rs780094 | C | T | 0.019 | Scott et al. 2012 | GCKR |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| FASTING INSULIN | rs1421085 | C | T | 0.02 | Scott et al. 2012 | FTO |
| FASTING INSULIN | rs983309 | T | G | 0.029 | Scott et al. 2012 | PPP1R3B |
| Favourable Adiposity | rs11045172 | C | A | 0.012 | Ji et al. 2019 | EBP2-PDE3A |
| Favourable Adiposity | rs11118306 | A | G | 0.023 | Ji et al. 2019 | LYPLAL1-SLC30A10 |
| Favourable Adiposity | rs13389219 | T | C | 0.023 | Ji et al. 2019 | GRB14-COBLL1 |
| Favourable Adiposity | rs1801282 | G | C | 0.031 | Ji et al. 2019 | PPARG |
| Favourable Adiposity | rs2267373 | C | T | 0.025 | Ji et al. 2019 | MAFF |
| Favourable Adiposity | rs2276936 | A | C | 0.016 | Ji et al. 2019 | FAM13A |
| Favourable Adiposity | rs2943653 | C | T | 0.032 | Ji et al. 2019 | NYAP2-IRS1 |
| Favourable Adiposity | rs2980888 | C | T | 0.006 | Ji et al. 2019 | TRIB1--[ |
| Favourable Adiposity | rs40271 | C | T | 0.021 | Ji et al. 2019 | ANKRD55-MAP3K1 |
| Favourable Adiposity | rs632057 | G | T | 0.009 | Ji et al. 2019 | CITED2 |
| Favourable Adiposity | rs7133378 | A | G | 0.026 | Ji et al. 2019 | DNAH10 |
| Favourable Adiposity | rs7258937 | T | C | 0.015 | Ji et al. 2019 | PEPD |
| Favourable Adiposity | rs972283 | A | G | 0.017 | Ji et al. 2019 | KLF14-MKLN1 |
| Favourable Adiposity | rs998584 | C | A | 0.016 | Ji et al. 2019 | VEGFA-C6orf223 |
| HDL CHOLESTEROL | rs1011731 | A | G | 0.015 | Liu et al. | DNM3:Intron |
| HDL CHOLESTEROL | rs1037378 | G | A | 0.015 | Liu et al. | PDE3B:Intron |
| HDL CHOLESTEROL | rs10483776 | A | G | 0.02 | Liu et al. | FUT8:Intron |
| HDL CHOLESTEROL | rs10861661 | A | C | 0.017 | Liu et al. | RIC8B:Intron |
| HDL CHOLESTEROL | rs10968576 | A | G | 0.017 | Liu et al. | LINGO2:Intron |
| HDL CHOLESTEROL | rs11553746 | T | C | 0.015 | Liu et al. | ACP1:Thr951le |
| HDL CHOLESTEROL | rs12055786 | C | T | 0.021 | Liu et al. | RGS17:Intron |
| HDL CHOLESTEROL | rs13379043 | C | T | 0.017 | Liu et al. | C14orf43:Intron |
| HDL CHOLESTEROL | rs146179438 | C | A | 0.063 | Liu et al. | CDC25A:Gln25His |
| HDL CHOLESTEROL | rs16928809 | G | A | 0.029 | Liu et al. | SLC22A18:Intron |
| HDL CHOLESTEROL | rs17189743 | A | G | 0.04 | Liu et al. | TSPYL6:Arg246Cys |
| HDL CHOLESTEROL | rs2074158 | T | C | 0.02 | Liu et al. | DHX58:GIn425Arg |
| HDL CHOLESTEROL | rs2303108 | T | C | 0.015 | Liu et al. | ZC3H4:Intron |
| HDL CHOLESTEROL | rs2785990 | C | T | 0.015 | Liu et al. | LYPLAL1:Intergenic |
| HDL CHOLESTEROL | rs28932178 | C | T | 0.02 | Liu et al. | NSD1:Ser457Pro |
| HDL CHOLESTEROL | rs35169799 | C | T | 0.039 | Liu et al. | PLCB3:Ser778Leu |
| HDL CHOLESTEROL | rs4871137 | G | T | 0.022 | Liu et al. | KCND3:Intergenic |
| HDL CHOLESTEROL | rs4976033 | A | G | 0.015 | Liu et al. | IGFN1:Intergenic |
| HDL CHOLESTEROL | rs622082 | A | G | 0.017 | Liu et al. | IGHMBP2:Thr671Ala |
| HDL CHOLESTEROL | rs7076938 | T | C | 0.019 | Liu et al. | PLOD1:Intergenic |
| HDL CHOLESTEROL | rs7136716 | G | A | 0.021 | Liu et al. | AVPR1B:Intergenic |
| HDL CHOLESTEROL | rs746463 | C | T | 0.017 | Liu et al. | ZC3H12C:Intron |
| HDL CHOLESTEROL | rs76116020 | A | G | 0.041 | Liu et al. | TMED6:Phe6Leu |
| HDL CHOLESTEROL | rs78074706 | G | A | 0.053 | Liu et al. | ANKS3:Arg286Trp |
| HDL CHOLESTEROL | rs8099014 | A | C | 0.015 | Liu et al. | VPS13D:Intergenic |
| HDL CHOLESTEROL | rs900399 | G | A | 0.019 | Liu et al. | SEMA4A:Intergenic |
| HDL CHOLESTEROL | rs9816226 | T | A | 0.028 | Liu et al. | B4GALT3:Intergenic |
| HDL CHOLESTEROL | rs10019888 | A | G | 0.027 | Willer et al. 2013 | C4orf52 |
| HDL CHOLESTEROL | rs1047891 | C | C | 0.027 | Willer et al. 2013 | CPS1 |
| HDL CHOLESTEROL | rs1121980 | G | A | 0.02 | Willer et al. 2013 | FTO |
| HDL CHOLESTEROL | rs11246602 | C | T | 0.034 | Willer et al. 2013 | OR4C46 |
| HDL CHOLESTEROL | rs11613352 | T | C | 0.028 | Willer et al. 2013 | LRP1 |
| HDL CHOLESTEROL | rs11869286 | C | G | 0.032 | Willer et al. 2013 | STARD3 |
| HDL CHOLESTEROL | rs12145743 | G | T | 0.02 | Willer et al. 2013 | HDGF, PMVK |
| HDL CHOLESTEROL | rs12328675 | C | T | 0.045 | Willer et al. 2013 | COBLL1 |
| HDL CHOLESTEROL | rs12678919 | G | A | 0.155 | Willer et al. 2013 | LPL |
| HDL CHOLESTEROL | rs12748152 | C | T | 0.051 | Willer et al. 2013 | PIGV, NROB2 |
| HDL CHOLESTEROL | rs12801636 | A | G | 0.024 | Willer et al. 2013 | KAT5 |
| HDL CHOLESTEROL | rs12967135 | G | A | 0.026 | Willer et al. 2013 | MC4R |
| HDL CHOLESTEROL | rs13076253 | A | C | 0.028 | Willer et al. 2013 | CPNE4 |
| HDL CHOLESTEROL | rs13107325 | C | T | 0.071 | Willer et al. 2013 | SLC39A8 |
| HDL CHOLESTEROL | rs13326165 | A | G | 0.029 | Willer et al. 2013 | STAB1 |
| HDL CHOLESTEROL | rs1532085 | A | G | 0.107 | Willer et al. 2013 | LIPC |
| HDL CHOLESTEROL | rs1689800 | A | G | 0.034 | Willer et al. 2013 | ZNF648 |
| HDL CHOLESTEROL | rs16942887 | A | G | 0.083 | Willer et al. 2013 | LCAT |
| HDL CHOLESTEROL | rs17145738 | T | C | 0.041 | Willer et al. 2013 | MLXIPL |

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| rs17173637 | T | C | 0.036 |
| :---: | :---: | :---: | :---: |
| rs174546 | C | T | 0.039 |
| rs17695224 | G | A | 0.029 |
| rs1800961 | C | T | 0.127 |
| rs181362 | C | T | 0.038 |
| rs1883025 | C | T | 0.07 |
| rs1936800 | C | T | 0.02 |
| rs2013208 | T | C | 0.025 |
| rs2290547 | G | A | 0.03 |
| rs2293889 | G | T | 0.031 |
| rs2602836 | A | G | 0.019 |
| rs2606736 | C | T | 0.025 |
| rs2652834 | G | A | 0.029 |
| rs2923084 | A | G | 0.026 |
| rs2925979 | C | T | 0.035 |
| rs2954029 | T | A | 0.04 |
| rs2972146 | G | T | 0.032 |
| rs3136441 | C | T | 0.055 |
| rs3764261 | A | C | 0.241 |
| rs3822072 | G | A | 0.025 |
| rs386000 | C | G | 0.048 |
| rs4129767 | A | G | 0.024 |
| rs4142995 | G | T | 0.026 |
| rs4148008 | C | G | 0.028 |
| rs4420638 | A | G | 0.067 |
| rs4650994 | G | A | 0.021 |
| rs4660293 | A | G | 0.035 |
| rs4731702 | T | C | 0.029 |
| rs4759375 | T | C | 0.056 |
| rs4765127 | T | G | 0.032 |
| rs4846914 | A | G | 0.048 |
| rs4917014 | G | T | 0.022 |
| rs4983559 | G | A | 0.02 |
| rs499974 | C | A | 0.026 |
| rs581080 | C | G | 0.042 |
| rs605066 | T | C | 0.028 |
| rs6065906 | T | C | 0.059 |
| rs6450176 | G | A | 0.025 |
| rs6805251 | T | C | 0.02 |
| rs702485 | G | A | 0.024 |
| rs7134375 | A | C | 0.021 |
| rs7134594 | T | C | 0.035 |
| rs7241918 | T | G | 0.09 |
| rs7255436 | A | C | 0.032 |
| rs731839 | A | G | 0.022 |
| rs737337 | T | C | 0.057 |
| rs7941030 | C | T | 0.028 |
| rs838880 | C | T | 0.048 |
| rs964184 | C | G | 0.107 |
| rs970548 | C | A | 0.026 |
| rs998584 | C | A | 0.026 |
| rs9987289 | G | A | 0.082 |
| rs1016988 | T | C | 0.02 |
| rs10885997 | G | A | 0.015 |
| rs11080150 | A | G | 0.019 |
| rs13146272 | C | A | 0.015 |
| rs13379043 | T | C | 0.018 |
| rs147032017 | C | T | 0.091 |
| rs1891110 | A | G | 0.021 |
| rs201148465 | C | A | 0.21 |
| rs201596848 | C | T | 0.255 |
| rs2076674 | C | T | 0.018 |
| rs2125345 | T | C | 0.024 |

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TMEM176A
FADS1, FADS2, FADS3
HAS1
HNF4A
UBE2L3
ABCA1
RSPO3
RBM5
SETD2
TRPS1
ADH5
ATG7
LACTB
AMPD3
CMIP
TRIB1
IRS1
LRP4
CETP
FAM13A
LILRA3
PGS1
SNX13
ABCA8
APOE
ANGPTL1
PABPC4
KLF14
SBNO1
ZNF664
GALNT2
IKZF1
ZBTB42, AKT1
MOGAT2, DGAT2
TTC39B
CITED2
PLTP
ARL15
GSK3B
DAGLB
PDE3A
MVK
LIPG
ANGPTL4
PEPD
ANGPTL8
UBASH3B
SCARB1
APOA1
MARCH8, ALOX5
VEGFA
PPP1R3B
CD101:Intergenic
PNLIPRP2:Gln387Arg
NF1:Intron
CYP4V2:Gln259Lys
C14orf43:Intron
ZFPM1:Asp91Asp
FAM24B:Pro2Leu
HIST1H1B:Ala6Ala
ZNF574:Arg734Cys
SLC25A17:Intron
UNK:Intron

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| rs2239619 | A | C | 0.018 | Liu et al. | HSPG2:Intergenic |
| :---: | :---: | :---: | :---: | :---: | :---: |
| rs28929474 | T | C | 0.081 | Liu et al. | SERPINA1:Glu366Lys |
| rs351855 | G | A | 0.018 | Liu et al. | FGFR4:Gly388Arg |
| rs3812594 | G | A | 0.018 | Liu et al. | SEC16A:Arg1039Cys |
| rs4745 | A | T | 0.015 | Liu et al. | EFNA1:Asp137Val |
| rs4809330 | A | G | 0.015 | Liu et al. | ZGPAT:Intron |
| rs6062343 | G | A | 0.014 | Liu et al. | TCEA2:Intron |
| rs61754230 | T | C | 0.057 | Liu et al. | RAB21:Ser224Phe |
| rs635634 | T | C | 0.069 | Liu et al. | IL6R:Intergenic |
| rs67710536 | C | A | 0.028 | Liu et al. | RPS6:Utr3 |
| rs6818397 | T | G | 0.022 | Liu et al. | RGS12:Intron |
| rs704 | A | G | 0.021 | Liu et al. | VTN:Thr400Met |
| rs77375493 | G | T | 0.3 | Liu et al. | JAK2 |
| rs9646133 | G | T | 0.019 | Liu et al. | FLAD1:Intergenic |
| rs976002 | G | A | 0.023 | Liu et al. | TMPRSS11E:Tyr303Cys |
| rs10102164 | A | G | 0.032 | Willer et al. 2013 | SOX17 |
| rs10401969 | T | C | 0.118 | Willer et al. 2013 | CILP2 |
| rs10490626 | G | A | 0.051 | Willer et al. 2013 | INSIG2 |
| rs11065987 | A | G | 0.027 | Willer et al. 2013 | BRAP |
| rs11136341 | G | A | 0.045 | Willer et al. 2013 | PLEC1 |
| rs11220462 | A | G | 0.059 | Willer et al. 2013 | ST3GAL4 |
| rs11563251 | T | C | 0.035 | Willer et al. 2013 | UGT1A1 |
| rs1169288 | C | A | 0.038 | Willer et al. 2013 | HNF1A |
| rs12027135 | T | A | 0.03 | Willer et al. 2013 | LDLRAP1 |
| rs1250229 | C | T | 0.024 | Willer et al. 2013 | FN1 |
| rs12670798 | C | T | 0.034 | Willer et al. 2013 | DNAH11 |
| rs12748152 | T | C | 0.05 | Willer et al. 2013 | PIGV, NROB2 |
| rs12916 | C | T | 0.073 | Willer et al. 2013 | HMGCR |
| rs1367117 | A | G | 0.119 | Willer et al. 2013 | APOB |
| rs1564348 | C | T | 0.048 | Willer et al. 2013 | LPA |
| rs17404153 | G | T | 0.034 | Willer et al. 2013 | ACAD11 |
| rs174546 | C | T | 0.051 | Willer et al. 2013 | FADS1, FADS2, FADS3 |
| rs1800562 | G | A | 0.062 | Willer et al. 2013 | HFE |
| rs1801689 | C | A | 0.103 | Willer et al. 2013 | APOH, PRXCA |
| rs2000999 | A | G | 0.065 | Willer et al. 2013 | HPR |
| rs2030746 | T | C | 0.021 | Willer et al. 2013 | LOC84931 |
| rs2072183 | C | G | 0.039 | Willer et al. 2013 | NPC1L1 |
| rs2081687 | T | C | 0.031 | Willer et al. 2013 | CYP7A1 |
| rs2131925 | T | G | 0.049 | Willer et al. 2013 | ANGPTL3 |
| rs2255141 | A | G | 0.03 | Willer et al. 2013 | GPAM |
| rs2328223 | C | A | 0.03 | Willer et al. 2013 | SNX5 |
| rs2479409 | G | A | 0.064 | Willer et al. 2013 | PCSK9 |
| rs2642442 | T | C | 0.036 | Willer et al. 2013 | MOSC1 |
| rs267733 | A | G | 0.033 | Willer et al. 2013 | ANXA9, CERS2 |
| rs2710642 | A | G | 0.024 | Willer et al. 2013 | EHBP1 |
| rs2902940 | A | G | 0.027 | Willer et al. 2013 | MAFB |
| rs2954029 | A | T | 0.056 | Willer et al. 2013 | TRIB1 |
| rs314253 | T | C | 0.024 | Willer et al. 2013 | DLG4 |
| rs3177928 | A | G | 0.045 | Willer et al. 2013 | HLA |
| rs364585 | G | A | 0.025 | Willer et al. 2013 | SPTLC3 |
| rs3757354 | C | T | 0.038 | Willer et al. 2013 | MYLIP |
| rs3764261 | C | A | 0.053 | Willer et al. 2013 | CETP |
| rs3780181 | A | G | 0.045 | Willer et al. 2013 | VLDLR |
| rs4253776 | G | A | 0.031 | Willer et al. 2013 | PPARA |
| rs4299376 | G | T | 0.081 | Willer et al. 2013 | ABCG5, ABCG58 |
| rs4420638 | G | A | 0.225 | Willer et al. 2013 | APOE |
| rs4530754 | A | G | 0.028 | Willer et al. 2013 | CSNK1G3 |
| rs4722551 | C | T | 0.039 | Willer et al. 2013 | MIR148A |
| rs4942486 | T | C | 0.024 | Willer et al. 2013 | BRCA2 |
| rs514230 | T | A | 0.036 | Willer et al. 2013 | IRF2BP2 |
| rs5763662 | T | C | 0.077 | Willer et al. 2013 | MTMR3 |
| rs6029526 | A | T | 0.044 | Willer et al. 2013 | TOP1 |
| rs629301 | T | G | 0.167 | Willer et al. 2013 | SORT1 |

HSPG2:Intergenic
PINA1:Glu366Lys

SEC16A:Arg1039Cys
EFNA1:Asp137Val
ZGPAT:Intron
TCEA2:Intron
RAB21:Ser224Phe
6R:Intergenic

RGS12:Intron
VTN:Thr400Met
JAK2
FLAD1:Intergenic
3Cys

CILP2
INSIG2

PLEC1
ST3GAL4
UGT1A1

LDLRAP1
FN1
DNAH11
PIGV, NROB2
HMGCR

LPA
ACAD11
FADS1, FADS2, FADS3

APOH, PRXCA
HPR

NPC1L1
CYP7A1
ANGPTL3
GPAM
SNX5

MOSC1
ANXA9, CERS2
EHBP1
MAFB

DLG4
HLA

MYLIP
CETP
PDARA
ABCG5, ABCG58
APOE
SNK1G3

BRCA2
IRF2BP2

TOP1
SORT1

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| rs6511720 | G | T | 0.221 |
| :---: | :---: | :---: | :---: |
| rs6882076 | C | T | 0.046 |
| rs7206971 | A | G | 0.029 |
| rs7640978 | C | T | 0.039 |
| rs8017377 | A | G | 0.03 |
| rs9488822 | A | T | 0.031 |
| rs964184 | G | C | 0.086 |
| rs9987289 | G | A | 0.071 |
| rs1813353 | T | C | 0.569 |
| rs2932538 | G | A | 0.388 |
| rs381815 | T | C | 0.575 |
| rs4373814 | C | G | 0.373 |
| rs4590817 | G | C | 0.646 |
| rs6015450 | G | A | 0.896 |
| rs7129220 | A | G | 0.619 |
| rs10077885 | C | A | 0.284 |
| rs10760117 | T | G | 0.283 |
| rs11128722 | G | A | 0.31 |
| rs11556924 | C | T | 0.271 |
| rs1156725 | C | T | 0.447 |
| rs11953630 | C | T | 0.412 |
| rs12247028 | G | A | 0.364 |
| rs12627651 | A | G | 0.391 |
| rs12656497 | C | T | 0.487 |
| rs12705390 | A | G | 0.619 |
| rs12940887 | T | C | 0.362 |
| rs12958173 | A | C | 0.361 |
| rs13107325 | C | T | 0.837 |
| rs1327235 | G | A | 0.395 |
| rs1361831 | C | T | 0.482 |
| rs1371182 | C | T | 0.444 |
| rs1458038 | T | C | 0.659 |
| rs1620668 | G | A | 0.535 |
| rs17010957 | C | T | 0.498 |
| rs17037390 | G | A | 0.908 |
| rs17608766 | C | T | 0.658 |
| rs1799945 | G | C | 0.627 |
| rs2291435 | C | T | 0.344 |
| rs2493134 | C | T | 0.413 |
| rs2521501 | T | A | 0.65 |
| rs2586886 | C | T | 0.404 |
| rs2594992 | C | A | 0.334 |
| rs2898290 | T | C | 0.377 |
| rs2969070 | G | A | 0.298 |
| rs3184504 | T | C | 0.598 |
| rs3735533 | C | T | 0.798 |
| rs3741378 | C | T | 0.486 |
| rs4247374 | C | T | 0.593 |
| rs4691707 | G | A | 0.349 |
| rs592373 | A | G | 0.484 |
| rs6271 | C | T | 0.591 |
| rs633185 | C | G | 0.565 |
| rs6442101 | T | C | 0.396 |
| rs6779380 | C | T | 0.439 |
| rs6919440 | G | A | 0.337 |
| rs7103648 | G | A | 0.335 |
| rs711737 | A | C | 0.334 |
| rs7213273 | G | A | 0.413 |
| rs740746 | A | G | 0.486 |
| rs7515635 | T | C | 0.307 |
| rs751984 | T | C | 0.407 |
| rs880315 | C | T | 0.475 |
| rs932764 | G | A | 0.495 |

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LDLR TIMD4 OSBPL7
CMTM6
NYNRIN
FRK
APOA1
PPP1R3B
CACNB2
MOV10
PLEKHA7
CACNB2
C10orf107
EDN3, GNAS
ADM
TRIM36
PSMD5
FGD5
ZC3HC1
PLEKHA7
EBF1
SYNPO2L
CRYAA, SIK1
NPR3, C5orf23
PIK3C
ZNF652
SETBP1
SLC39A8
JAG1
RSPO3
FIGN, GRB14
FGF5
ST7L, CAPZA1, MOV10
ARHGAP24
MTHFR, NPPB
GOSR2
HFE
TBC1D1, FLJ13197
AGT
FURIN, FES
KCNK3
HRH1, ATG7
BLK, GATA4
CHST12, LFNG
SH2B3
HOTTIP, EVX
SIPA1
INSR
GUCY1A3, GUCY1B3
LSP1, TNNT3
DBH
FLJ32810, TMEM133
MAP4
MECOM
ZNF318, ABCC10
RAPSN, PSMC3, SLC39A13
SLC4A7
PLCD3
ADRB1
HIVEP3
LRRC10B
CASZ1
PLCE1

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| rs943037 | C | T | 1.133 |
| :---: | :---: | :---: | :---: |
| rs1008058 | A | G | 0.554 |
| rs11229457 | C | T | 0.312 |
| rs1378942 | C | A | 0.613 |
| rs17249754 | G | A | 0.928 |
| rs34591516 | T | C | 0.636 |
| rs35529250 | C | T | 1.537 |
| rs4387287 | A | C | 0.338 |
| rs4728142 | G | A | 0.224 |
| rs61760904 | T | C | 1.499 |
| rs7406910 | C | T | 0.456 |
| rs805303 | G | A | 0.376 |
| rs9349379 | A | G | 0.289 |
| rs10059921 | G | T | 0.526 |
| rs10922502 | G | A | 0.382 |
| rs112184198 | G | A | 0.659 |
| rs11643209 | G | T | 0.339 |
| rs12941318 | C | T | 0.269 |
| rs13112725 | C | G | 0.435 |
| rs13238550 | A | G | 0.331 |
| rs13420463 | A | G | 0.356 |
| rs2467099 | C | T | 0.307 |
| rs35199222 | A | G | 0.322 |
| rs3820068 | A | G | 0.425 |
| rs55780018 | C | T | 0.391 |
| rs6487543 | A | G | 0.3 |
| rs6595838 | A | G | 0.344 |
| rs6911827 | T | C | 0.296 |
| rs7562 | T | C | 0.263 |
| rs78648104 | C | T | 0.481 |
| rs8016306 | A | G | 0.335 |
| rs894344 | G | A | 0.258 |
| rs9549328 | T | C | 0.318 |
| rs9888615 | C | T | 0.318 |
| rs1011731 | G | A | 0.015 |
| rs10861661 | C | A | 0.019 |
| rs138358301 | G | A | 0.15 |
| rs26008 | T | C | 0.028 |
| rs2785990 | T | C | 0.016 |
| rs35169799 | T | C | 0.038 |
| rs35665085 | A | G | 0.032 |
| rs3769823 | G | A | 0.017 |
| rs3803357 | C | A | 0.017 |
| rs3927680 | T | A | 0.018 |
| rs3947 | A | G | 0.024 |
| rs41274050 | T | C | 0.1 |
| rs41302559 | G | A | 0.154 |
| rs4976033 | G | A | 0.018 |
| rs6062343 | G | A | 0.018 |
| rs7157785 | T | G | 0.023 |
| rs7901016 | C | T | 0.042 |
| rs7946 | C | T | 0.016 |
| rs797486 | A | C | 0.02 |
| rs900399 | A | G | 0.014 |
| rs10401969 | T | C | 0.121 |
| rs10761731 | A | T | 0.031 |
| rs11613352 | C | T | 0.028 |
| rs11649653 | C | G | 0.027 |
| rs11776767 | C | G | 0.022 |
| rs1260326 | T | C | 0.115 |
| rs12678919 | A | G | 0.17 |
| rs12748152 | T | C | 0.037 |
| rs13238203 | C | T | 0.059 |

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CYP17A1, NT5C2
PRDM6
OR5B12
CYP1A1-ULK3
ATP2B1
GPR20
RBM47
OBFC1
Intergenic
RRAS
HOXB7
BAT2, BAT5
PHACTR1
TMEM161B
GTF2B
PAX2
CFDP1
CRK
NPNT
MKLN1
PRKD3
ACOX1
ABHD17C
CELA2A
METTL21A, SSPN/ITPR2
FBN2
CASC15
FOSL2
TFAP2D
PPP2R5E
ZFAT
MCF2L
FERMT2
DNM3:Intron
RIC8B:Intron
SLC25A30:Phe280Leu
FNIP1:GIn620Arg
LYPLAL1:Intergenic
PLCB3:Ser778Leu
CECR5:Thr149Met
CASP8:Lys14Arg
BAHD1:GIn298Lys
OR6P1:Intergenic
CTSB:Utr3
A1CF:Gly398Ser
PCK1:Arg483Gln
IGFN1:Intergenic
TCEA2:Intron
NPR1:Intergenic
CCDC109A:Intron
PEMT:Val212Met
ADAR:Intergenic
SEMA4A:Intergenic
CILP2
JMJD1C
LRP1
CTF1
PINX1
GCKR
LPL
PIGV, NROB2
TYW1B

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rs4846914 G
rs5756931 T
rs6065906 C
rs645040 T
rs6831256 G
rs6882076 C
rs7248104 G
rs731839 G
rs964184 G
rs9686661 T
rs9930333 G
rs998584 A
rs6054
rs17867832 T
rs3734621 C
rs3786897 A
rs831571 C
rs9470794 T
rs2233580 T
rs6813195
rs10278336 A
rs12242953 G
rs16861329 C
rs2007084 G
rs4812829 A
rs10401969
rs10758593
rs10811661 T
rs10830963 G
rs10842994 C
rs10923931 T
rs1111875 C
rs11257655 T
rs11634397 G
rs11651052 A
rs11717195 T
rs12427353 G
rs12571751 A
rs12899811 G
rs12970134 A G 0.076961041
rs13389219 C T 0.067658648
rs1359790 G A 0.076961041
rs1496653 A G 0.086177696

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NAT2
LIPC
MLXIPL
FADS1, FADS2, FADS3
AKR1C4
RSPO3
CYP26A1
ANGPTL3
HLA-B
CAPN3
FRMD5
TRIB1
IRS1
PDXDC1
CETP
MET
KLHL8
MIR148A
ZNF664
GALNT2
PLA2G6
PLTP
MSL2L1
LRPAP1
TIMD4
INSR
PEPD
MPP3
APOA1
MAP3K1
FTO
VEGFA
FGB:Pro206Leu
GRM8
KIF6
PEPD
PSMD6
ZFND3
PAX4
TMEM154
MOB2
SRGN
ST6GAL1
ANPEP
HNF4A
CILP2
GLIS3
CDKN2A/B
MTNR1B
KLHDC5
NOTCH2
HHEX, IDE
CDC123/CAMK1D
ZFAND6
HNF1B
ADCY5
HNF1A
ZMIZ1
PRC1
MC4R
GRB14
SPRY2
UBE2E2

TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES TYPE 2 DIABETES
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| rs1552224 | A | C | 0.104360015 | Morris et al. 2012 |
| :---: | :---: | :---: | :---: | :---: |
| rs163184 | G | T | 0.086177696 | Morris et al. 2012 |
| rs17168486 | T | C | 0.104360015 | Morris et al. 2012 |
| rs17791513 | A | G | 0.113328685 | Morris et al. 2012 |
| rs1801282 | C | G | 0.122217633 | Morris et al. 2012 |
| rs2075423 | G | T | 0.067658648 | Morris et al. 2012 |
| rs2261181 | T | C | 0.122217633 | Morris et al. 2012 |
| rs243088 | T | A | 0.067658648 | Morris et al. 2012 |
| rs2796441 | G | A | 0.067658648 | Morris et al. 2012 |
| rs2943640 | C | A | 0.09531018 | Morris et al. 2012 |
| rs3802177 | G | A | 0.131028262 | Morris et al. 2012 |
| rs4402960 | T | G | 0.122217633 | Morris et al. 2012 |
| rs4458523 | G | T | 0.09531018 | Morris et al. 2012 |
| rs4502156 | T | C | 0.058268908 | Morris et al. 2012 |
| rs459193 | G | A | 0.076961041 | Morris et al. 2012 |
| rs516946 | C | T | 0.086177696 | Morris et al. 2012 |
| rs5215 | C | T | 0.067658648 | Morris et al. 2012 |
| rs6795735 | C | T | 0.076961041 | Morris et al. 2012 |
| rs6878122 | G | A | 0.09531018 | Morris et al. 2012 |
| rs7177055 | A | G | 0.076961041 | Morris et al. 2012 |
| rs7202877 | T | G | 0.113328685 | Morris et al. 2012 |
| rs7756992 | G | A | 0.157003749 | Morris et al. 2012 |
| rs7845219 | T | C | 0.058268908 | Morris et al. 2012 |
| rs7903146 | T | C | 0.329303747 | Morris et al. 2012 |
| rs7955901 | C | T | 0.067658648 | Morris et al. 2012 |
| rs8108269 | G | T | 0.067658648 | Morris et al. 2012 |
| rs849135 | G | A | 0.104360015 | Morris et al. 2012 |
| rs9936385 | C | T | 0.122217633 | Morris et al. 2012 |
| rs2334499 | T | C | 0.039220713 | PMID: 20016592 |
| rs7593730 | C | T | 0.104360015 | Qi et al. 2010 |
| rs76895963 | T | G | 0.634878032 | Steinthorsdottir et al. 2014 |
| rs16927668 | T | C | 0.039220713 | Tsai et al. 2010 |
| rs2447090 | A | G | 0.039220713 | Tsai et al. 2010 |
| rs13233731 | G | A | 0.048790164 | Voight et al. 2010 |
| rs10049088 | C | miss | 0.029 | Pulit et al. 2019 |
| rs10054063 | T | miss | 0.027 | Pulit et al. 2019 |
| rs10055995 | C | miss | 0.011 | Pulit et al. 2019 |
| rs10100423 | T | miss | 0.042 | Pulit et al. 2019 |
| rs10100533 | A | miss | 0.014 | Pulit et al. 2019 |
| rs10249651 | C | miss | 0.015 | Pulit et al. 2019 |
| rs1029472 | G | miss | 0.025 | Pulit et al. 2019 |
| rs1029645 | G | miss | 0.013 | Pulit et al. 2019 |
| rs1035942 | A | miss | 0.014 | Pulit et al. 2019 |
| rs1045241 | C | miss | 0.019 | Pulit et al. 2019 |
| rs10462028 | A | miss | 0.019 | Pulit et al. 2019 |
| rs10463416 | A | miss | 0.014 | Pulit et al. 2019 |
| rs10502148 | C | miss | 0.023 | Pulit et al. 2019 |
| rs10507524 | C | miss | 0.018 | Pulit et al. 2019 |
| rs1051684 | A | miss | 0.013 | Pulit et al. 2019 |
| rs1057119 | C | miss | 0.013 | Pulit et al. 2019 |
| rs10745659 | G | miss | 0.013 | Pulit et al. 2019 |
| rs10778504 | T | miss | 0.016 | Pulit et al. 2019 |
| rs10799424 | T | miss | 0.013 | Pulit et al. 2019 |
| rs10808546 | C | miss | 0.016 | Pulit et al. 2019 |
| rs10817896 | T | miss | 0.013 | Pulit et al. 2019 |
| rs10820747 | A | miss | 0.027 | Pulit et al. 2019 |
| rs10827226 | T | miss | 0.02 | Pulit et al. 2019 |
| rs10842707 | T | miss | 0.034 | Pulit et al. 2019 |
| rs10843804 | T | miss | 0.015 | Pulit et al. 2019 |
| rs10878367 | A | miss | 0.019 | Pulit et al. 2019 |
| rs10880823 | C | miss | 0.013 | Pulit et al. 2019 |
| rs10887759 | A | miss | 0.017 | Pulit et al. 2019 |
| rs10913257 | G | miss | 0.011 | Pulit et al. 2019 |

ARAP1
KCNQ1
DGKB
TLE4
PPARG
PROX1
HMGA2
BCL11A
TLE1
IRS1
SLC30A8
IGF2BP2
WFS1
C2CD4A
ANKRD55
ANK1
KCNJ11
ADAMTS9
ZBED3
HMG2OA
BCAR1
CDKAL1
TP53INP1
TCF7L2
TSPAN8, LGR5
GIPR
JAZF1
FTO
RBMS1/ITGB6
CCND2
PTPRD
MNT
KLF14
Not available
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| rs10919388 | C | miss | 0.033 |
| :---: | :---: | :---: | :---: |
| rs10923724 | T | miss | 0.035 |
| rs10963067 | C | miss | 0.021 |
| rs10980797 | G | miss | 0.018 |
| rs11042077 | A | miss | 0.012 |
| rs1105881 | G | miss | 0.016 |
| rs11074934 | T | miss | 0.012 |
| rs11078594 | G | miss | 0.015 |
| rs11082430 | C | miss | 0.013 |
| rs11085744 | T | miss | 0.011 |
| rs11088991 | T | miss | 0.013 |
| rs1111875 | C | miss | 0.011 |
| rs11129657 | C | miss | 0.015 |
| rs11134029 | T | miss | 0.014 |
| rs11187537 | C | miss | 0.016 |
| rs11204762 | A | miss | 0.014 |
| rs11205773 | T | miss | 0.019 |
| rs11235 | C | miss | 0.022 |
| rs112907088 | G | miss | 0.041 |
| rs1139653 | A | miss | 0.018 |
| rs1144 | C | miss | 0.015 |
| rs114760566 | A | miss | 0.093 |
| rs11574514 | C | miss | 0.029 |
| rs11592754 | C | miss | 0.022 |
| rs11670056 | C | miss | 0.024 |
| rs11722554 | G | miss | 0.033 |
| rs11724804 | G | miss | 0.017 |
| rs11746028 | C | miss | 0.014 |
| rs11747001 | A | miss | 0.017 |
| rs11757455 | G | miss | 0.022 |
| rs11770285 | C | miss | 0.031 |
| rs11786566 | G | miss | 0.011 |
| rs11897119 | C | miss | 0.014 |
| rs1190982 | T | miss | 0.016 |
| rs12138803 | T | miss | 0.025 |
| rs1223581 | T | miss | 0.011 |
| rs12325187 | C | miss | 0.013 |
| rs12419064 | G | miss | 0.014 |
| rs12435790 | A | miss | 0.021 |
| rs12441543 | G | miss | 0.019 |
| rs12442323 | C | miss | 0.015 |
| rs12454712 | T | miss | 0.017 |
| rs12459350 | A | miss | 0.014 |
| rs12494105 | G | miss | 0.012 |
| rs1250259 | T | miss | 0.016 |
| rs12527712 | T | miss | 0.034 |
| rs12543555 | G | miss | 0.014 |
| rs12608426 | A | miss | 0.025 |
| rs12608504 | A | miss | 0.026 |
| rs12684047 | T | miss | 0.015 |
| rs12686771 | T | miss | 0.022 |
| rs12692387 | C | miss | 0.013 |
| rs12694042 | T | miss | 0.012 |
| rs12774134 | C | miss | 0.019 |
| rs12823266 | A | miss | 0.013 |
| rs12828318 | A | miss | 0.017 |
| rs1294432 | T | miss | 0.025 |
| rs13010546 | T | miss | 0.014 |
| rs13107325 | C | miss | 0.031 |
| rs13137905 | T | miss | 0.013 |
| rs13198178 | C | miss | 0.031 |
| rs13223034 | C | miss | 0.013 |
| rs13234914 | G | miss | 0.013 |

Pulit et al. 2019
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| rs13256367 | A | miss | 0.018 |
| :---: | :---: | :---: | :---: |
| rs1328757 | T | miss | 0.014 |
| rs1334576 | G | miss | 0.017 |
| rs13379794 | A | miss | 0.011 |
| rs1345203 | T | miss | 0.026 |
| rs1364422 | T | miss | 0.016 |
| rs1385167 | G | miss | 0.027 |
| rs139271800 | A | miss | 0.239 |
| rs140201358 | G | miss | 0.085 |
| rs1406948 | G | miss | 0.016 |
| rs144033177 | C | miss | 0.053 |
| rs1440372 | C | miss | 0.016 |
| rs144926207 | T | miss | 0.032 |
| rs145878042 | A | miss | 0.081 |
| rs146182298 | T | miss | 0.031 |
| rs1481801 | A | miss | 0.012 |
| rs1485745 | T | miss | 0.012 |
| rs1494204 | C | miss | 0.015 |
| rs149921263 | A | miss | 0.04 |
| rs150841499 | C | miss | 0.02 |
| rs1511022 | T | miss | 0.017 |
| rs1522811 | C | miss | 0.013 |
| rs1541681 | G | miss | 0.012 |
| rs1561 | T | miss | 0.022 |
| rs1569135 | A | miss | 0.021 |
| rs1635853 | T | miss | 0.016 |
| rs16907277 | G | miss | 0.023 |
| rs16976826 | T | miss | 0.02 |
| rs16978854 | G | miss | 0.033 |
| rs17067999 | C | miss | 0.016 |
| rs17101456 | G | miss | 0.025 |
| rs17154889 | C | miss | 0.016 |
| rs17289035 | A | miss | 0.014 |
| rs17311057 | T | miss | 0.015 |
| rs17326656 | T | miss | 0.015 |
| rs17369710 | C | miss | 0.012 |
| rs17417407 | T | miss | 0.014 |
| rs174829 | G | miss | 0.014 |
| rs17509001 | C | miss | 0.016 |
| rs17511102 | T | miss | 0.02 |
| rs1757471 | T | miss | 0.015 |
| rs17703354 | C | miss | 0.02 |
| rs17703883 | C | miss | 0.015 |
| rs17764730 | C | miss | 0.016 |
| rs1800978 | C | miss | 0.026 |
| rs1805740 | G | miss | 0.018 |
| rs180958337 | T | miss | 0.088 |
| rs1893781 | A | miss | 0.018 |
| rs1979527 | A | miss | 0.013 |
| rs1997833 | C | miss | 0.014 |
| rs2012485 | C | miss | 0.029 |
| rs2027982 | C | miss | 0.012 |
| rs2028386 | G | miss | 0.013 |
| rs2047937 | C | miss | 0.015 |
| rs2061708 | C | miss | 0.016 |
| rs2075665 | A | miss | 0.011 |
| rs2124307 | C | miss | 0.013 |
| rs2145272 | G | miss | 0.025 |
| rs2158828 | G | miss | 0.014 |
| rs2167750 | T | miss | 0.027 |
| rs2200155 | G | miss | 0.014 |
| rs2222543 | G | miss | 0.015 |
| rs2236519 | A | miss | 0.03 |

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| rs2272790 | G | miss | 0.013 |
| :---: | :---: | :---: | :---: |
| rs2277339 | G | miss | 0.022 |
| rs227733 | A | miss | 0.013 |
| rs2279469 | C | miss | 0.013 |
| rs2294239 | A | miss | 0.024 |
| rs2294823 | T | miss | 0.012 |
| rs2299253 | T | miss | 0.012 |
| rs2373078 | T | miss | 0.022 |
| rs2376585 | C | miss | 0.018 |
| rs2387280 | A | miss | 0.018 |
| rs2398893 | A | miss | 0.015 |
| rs2503100 | G | miss | 0.025 |
| rs2524163 | T | miss | 0.024 |
| rs2526886 | T | miss | 0.014 |
| rs2529411 | G | miss | 0.011 |
| rs2595004 | C | miss | 0.016 |
| rs2602680 | T | miss | 0.012 |
| rs2603229 | T | miss | 0.012 |
| rs2701523 | A | miss | 0.013 |
| rs270960 | A | miss | 0.011 |
| rs2786198 | A | miss | 0.013 |
| rs2791550 | G | miss | 0.037 |
| rs2836141 | T | miss | 0.015 |
| rs28408682 | G | miss | 0.012 |
| rs28451064 | A | miss | 0.018 |
| rs2898237 | A | miss | 0.012 |
| rs2925979 | T | miss | 0.027 |
| rs2970332 | A | miss | 0.016 |
| rs299615 | G | miss | 0.015 |
| rs2997447 | G | miss | 0.014 |
| rs3110697 | A | miss | 0.012 |
| rs3218121 | A | miss | 0.022 |
| rs322396 | A | miss | 0.012 |
| rs332105 | G | miss | 0.014 |
| rs34000 | T | miss | 0.014 |
| rs34312154 | A | miss | 0.019 |
| rs34905952 | A | miss | 0.021 |
| rs352300 | C | miss | 0.011 |
| rs35344256 | A | miss | 0.014 |
| rs35419826 | G | miss | 0.016 |
| rs35710478 | C | miss | 0.012 |
| rs357438 | G | miss | 0.011 |
| rs3731861 | C | miss | 0.011 |
| rs3741378 | C | miss | 0.022 |
| rs3757298 | C | miss | 0.021 |
| rs3761706 | A | miss | 0.032 |
| rs3786897 | G | miss | 0.028 |
| rs3792751 | T | miss | 0.014 |
| rs3803042 | A | miss | 0.027 |
| rs3807947 | T | miss | 0.014 |
| rs3851294 | G | miss | 0.026 |
| rs3936510 | T | miss | 0.03 |
| rs402294 | A | miss | 0.014 |
| rs41277978 | A | miss | 0.073 |
| rs4293945 | A | miss | 0.012 |
| rs4371408 | A | miss | 0.016 |
| rs4372913 | G | miss | 0.016 |
| rs4420638 | A | miss | 0.023 |
| rs4474021 | T | miss | 0.012 |
| rs4489410 | C | miss | 0.012 |
| rs4558863 | C | miss | 0.021 |
| rs4646342 | G | miss | 0.017 |
| rs4684857 | C | miss | 0.021 |

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| rs4686696 | A | miss | 0.015 |
| :---: | :---: | :---: | :---: |
| rs4773173 | A | miss | 0.015 |
| rs4789261 | C | miss | 0.029 |
| rs4794033 | G | miss | 0.019 |
| rs4902630 | A | miss | 0.012 |
| rs4951588 | C | miss | 0.012 |
| rs4964058 | A | miss | 0.011 |
| rs4964656 | G | miss | 0.016 |
| rs541091 | G | miss | 0.02 |
| rs55747707 | G | miss | 0.024 |
| rs55920843 | T | miss | 0.086 |
| rs56185013 | G | miss | 0.017 |
| rs56196860 | C | miss | 0.036 |
| rs56271783 | C | miss | 0.059 |
| rs598104 | T | miss | 0.014 |
| rs59888683 | T | miss | 0.014 |
| rs6018291 | G | miss | 0.014 |
| rs6040229 | G | miss | 0.011 |
| rs6047259 | T | miss | 0.01 |
| rs6054471 | T | miss | 0.012 |
| rs62012773 | G | miss | 0.017 |
| rs62070804 | T | miss | 0.047 |
| rs62271373 | A | miss | 0.041 |
| rs62621197 | C | miss | 0.036 |
| rs634869 | T | miss | 0.023 |
| rs6426912 | T | miss | 0.019 |
| rs6432188 | T | miss | 0.014 |
| rs6480914 | A | miss | 0.013 |
| rs6556301 | T | miss | 0.021 |
| rs664532 | T | miss | 0.013 |
| rs6658424 | T | miss | 0.014 |
| rs6688233 | T | miss | 0.021 |
| rs6705646 | A | miss | 0.025 |
| rs6721459 | G | miss | 0.018 |
| rs6752964 | C | miss | 0.019 |
| rs6795831 | A | miss | 0.035 |
| rs6853254 | T | miss | 0.017 |
| rs6859752 | T | miss | 0.012 |
| rs6867518 | C | miss | 0.018 |
| rs6872807 | T | miss | 0.011 |
| rs6905288 | A | miss | 0.044 |
| rs6932767 | T | miss | 0.015 |
| rs6940715 | A | miss | 0.022 |
| rs6985478 | A | miss | 0.015 |
| rs699370 | C | miss | 0.013 |
| rs7003062 | C | miss | 0.012 |
| rs7020604 | A | miss | 0.013 |
| rs7070749 | A | miss | 0.014 |
| rs7086377 | T | miss | 0.012 |
| rs7102 | C | miss | 0.012 |
| rs711076 | C | miss | 0.012 |
| rs711869 | G | miss | 0.019 |
| rs7119797 | C | miss | 0.013 |
| rs71439172 | G | miss | 0.023 |
| rs71511786 | A | miss | 0.023 |
| rs715300 | T | miss | 0.014 |
| rs717795 | C | miss | 0.02 |
| rs7198287 | C | miss | 0.014 |
| rs7213608 | C | miss | 0.012 |
| rs7225453 | C | miss | 0.015 |
| rs7235010 | A | miss | 0.019 |
| rs7252102 | G | miss | 0.014 |
| rs727428 | T | miss | 0.016 |

Pulit et al. 2019
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| rs7279347 | G | miss | 0.012 |
| :---: | :---: | :---: | :---: |
| rs72823057 | C | miss | 0.029 |
| rs72877579 | C | miss | 0.035 |
| rs72959041 | A | miss | 0.162 |
| rs73001065 | C | miss | 0.022 |
| rs73094710 | T | miss | 0.02 |
| rs7350438 | C | miss | 0.012 |
| rs73858966 | A | miss | 0.024 |
| rs73942938 | C | miss | 0.015 |
| rs7395513 | G | miss | 0.021 |
| rs740838 | C | miss | 0.043 |
| rs747249 | A | miss | 0.011 |
| rs7492628 | G | miss | 0.023 |
| rs7521902 | C | miss | 0.013 |
| rs7530102 | A | miss | 0.012 |
| rs7554947 | C | miss | 0.015 |
| rs755643 | G | miss | 0.012 |
| rs757081 | G | miss | 0.011 |
| rs757608 | A | miss | 0.019 |
| rs7585974 | C | miss | 0.019 |
| rs7680787 | T | miss | 0.014 |
| rs7708285 | G | miss | 0.013 |
| rs7721054 | T | miss | 0.017 |
| rs7744833 | A | miss | 0.012 |
| rs7795371 | A | miss | 0.017 |
| rs7798002 | T | miss | 0.032 |
| rs780159 | G | miss | 0.016 |
| rs7827182 | G | miss | 0.017 |
| rs7854560 | T | miss | 0.012 |
| rs7903146 | T | miss | 0.018 |
| rs7932891 | A | miss | 0.014 |
| rs7945962 | A | miss | 0.011 |
| rs79664277 | A | miss | 0.021 |
| rs797486 | A | miss | 0.037 |
| rs7993238 | C | miss | 0.012 |
| rs801593 | G | miss | 0.012 |
| rs8024294 | A | miss | 0.018 |
| rs8054299 | C | miss | 0.015 |
| rs805768 | T | miss | 0.018 |
| rs8066985 | A | miss | 0.023 |
| rs8074638 | A | miss | 0.016 |
| rs8080903 | C | miss | 0.015 |
| rs8103017 | G | miss | 0.02 |
| rs8126001 | C | miss | 0.016 |
| rs8142329 | G | miss | 0.017 |
| rs821100 | G | miss | 0.016 |
| rs848286 | T | miss | 0.012 |
| rs863750 | T | miss | 0.037 |
| rs889129 | T | miss | 0.02 |
| rs905938 | T | miss | 0.024 |
| rs910071 | C | miss | 0.017 |
| rs910382 | G | miss | 0.019 |
| rs917191 | C | miss | 0.014 |
| rs917681 | T | miss | 0.012 |
| rs930653 | A | miss | 0.011 |
| rs9341990 | A | miss | 0.015 |
| rs9388766 | C | miss | 0.017 |
| rs9415106 | A | miss | 0.014 |
| rs9435732 | C | miss | 0.013 |
| rs951252 | G | miss | 0.019 |
| rs9644033 | A | miss | 0.022 |
| rs9647379 | G | miss | 0.015 |
| rs9678859 | A | miss | 0.019 |

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| WAIST HIP RATIO (ADJUSTED BY BMI) | rs975385 | C | miss | 0.011 | Pulit et al. 2019 | Not available |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| WAIST HIP RATIO (ADJUSTED BY BMI) | rs9909443 | C | miss | 0.014 | Pulit et al. 2019 | Not available |

Supplementary table 3. ACR results of meta analysis of multivariate Mendelian randomization results for lipids adjusted by other lipids' betas in UK Biobank and CKDGen and in the two studies individually. 95\% confidence intervals in brackets.

Meta analysis

| Trait | Beta IVW | P IVW | Beta Egger | P Egger | Beta WM | P WM | Beta PWM | P PWM |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| TRIGLYCERIDES adjusted by LDL CHOLESTEROL and HDL CHOLESTEROL | 0.094 (0.073, 0.115) | $<1 \times \mathrm{E}-15$ | 0.112 (0.081, 0.144) | 1.3E-02 | 0.052 (0.033, 0.071) | 1.1E-07 | 0.048 (0.029, 0.068) | 1.1E-06 |
| HDL CHOLESTEROL adjusted by TRIGLYCERIDES and LDL CHOLESTEROL | 0.011 (-0.005, 0.028) | 1.7E-01 | 0.029 (0.006, 0.052) | 1.3E-02 | $0.008(-0.007,0.024)$ | 3.0E-01 | -0.008 (-0.028, 0.012) | 4.3E-01 |
| LDL CHOLESTEROL adjusted by HDL CHOLESTEROL and TRIGLYCERIDES | 0.018 (0.001, 0.035) | 3.4E-02 | $0.014(-0.012,0.040)$ | 3.0E-01 | 0.029 (0.014, 0.045) | $1.8 \mathrm{E}-04$ | 0.032 (0.016, 0.048) | 9.6E-05 |

UK Biobank

| Trait | Beta IVW | PIVW | Beta Egger | P Egger | Beta WM | P WM | Beta PWM | P PWM |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| TRIGLYCERIDES adjusted by LDL CHOLESTEROL and HDL CHOLESTEROL | 0.069 (0.040, 0.098) | 2.1E-05 | 0.092 (0.049, 0.134) | 1.1E-04 | 0.048 (0.027, 0.070) | 1.0E-05 | 0.044 (0.022, 0.066) | 8.5E-05 |
| HDL CHOLESTEROL adjusted by TRIGLYCERIDES and LDL CHOLESTEROL | 0.003 (-0.018, 0.024) | 7.6E-01 | 0.017 (-0.014, 0.048) | $2.8 \mathrm{E}-01$ | $0.002(-0.016,0.019)$ | 8.6E-01 | -0.035 (-0.060, -0.009) | 8.6E-03 |
| LDL CHOLESTEROL adjusted by HDL CHOLESTEROL and TRIGLYCERIDES | 0.015 (-0.004, 0.034) | 1.2E-01 | 0.026 (-0.004, 0.055) | 9.1E-02 | 0.032 (0.016, 0.048) | 1.1E-04 | 0.033 (0.016, 0.050) | 1.5E-04 |

## CKDGen

| Trait | Beta IVW | P IVW | Beta Egger | P Egger | Beta WM | P WM | Beta PWM |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| TRIGLYCERIDES adjusted by | $0.123(0.092,0.154)$ | $4.6 \mathrm{E}-10$ | $0.136(0.091,0.181)$ | $3.6 \mathrm{E}-07$ | $0.064(0.023,0.106)$ | $2.5 \mathrm{E}-03$ | $0.064(0.022,0.106)$ |
| LDL CHOLESTEROL and HDL <br> CHOLESTEROL | $2.8 \mathrm{E}-03$ |  |  |  |  |  |  |


| HDL CHOLESTEROL adjusted <br> by TRIGLYCERIDES and LDL <br> CHOLESTEROL | $0.024(-0.002,0.049)$ | $7.8 \mathrm{E}-02$ | $0.044(0.010,0.079)$ | $1.4 \mathrm{E}-02$ | $0.031(-0.002,0.063)$ | $6.4 \mathrm{E}-02$ | $0.031(0.000,0.062)$ | $5.4 \mathrm{E}-02$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| LDL CHOLESTEROL adjusted      <br> by HDL CHOLESTEROL and <br> TRIGLYCERIDES $0.028(-0.007,0.064)$ $1.2 \mathrm{E}-01$ $-0.031(-0.012,0.040)$ $3.0 \mathrm{E}-01$ $0.029(-0.047,0.056)$ | $8.6 \mathrm{E}-01$ | $0.026(-0.027,0.080)$ | $3.4 \mathrm{E}-01$ |  |  |  |  |  |

IVW = inverse variance weighted instrumental variable analysis, $W M=$ weighted median analysis, $P W M=$ penalised weighted median analysis.

Supplementary Table 4. UK Biobank and CKDGen grs and two sample Mendelian randomization results between investigated traits and ACR.

| Trait | Beta grs | SE grs | P grs | Beta IVW | SE IVW | P IVW | Beta <br> Egger | $\begin{gathered} \text { SE } \\ \text { Egger } \end{gathered}$ | P Egger | $\begin{aligned} & \text { Egger int } \\ & p \end{aligned}$ | Beta <br> WM | SE WM | P WM | Beta PWM | SE PWM | P PWM |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Diastolic BP | 0.0839 | 0.0105 | $1.4 \mathrm{E}-15$ | 0.0075 | 0.0018 | 7.6E-05 | 0.0011 | 0.0051 | 8.3E-01 | 1.83E-01 | 0.0080 | 0.0016 | 1.0E-06 | 0.0057 | 0.0021 | 5.9E-03 |
| Systolic BP | 0.0835 | 0.0115 | 4.7E-13 | 0.0035 | 0.0012 | 5.1E-03 | 0.0035 | 0.0038 | $3.6 \mathrm{E}-01$ | $9.98 \mathrm{E}-01$ | 0.0046 | 0.0010 | $6.2 \mathrm{E}-06$ | 0.0037 | 0.0014 | $6.5 \mathrm{E}-03$ |
| HDL cholesterol | -0.0198 | 0.0065 | $2.4 \mathrm{E}-03$ | -0.0133 | 0.0122 | $2.8 \mathrm{E}-01$ | -0.0041 | 0.0179 | 8.2E-01 | 4.84E-01 | 0.0087 | 0.0091 | $3.4 \mathrm{E}-01$ | -0.0058 | 0.0171 | 7.4E-01 |
| LDL cholesterol | 0.0204 | 0.0059 | 4.9E-04 | 0.0271 | 0.0157 | $1.3 \mathrm{E}-02$ | 0.0361 | 0.0160 | $2.8 \mathrm{E}-02$ | 4.53E-01 | 0.0334 | 0.0088 | $1.4 \mathrm{E}-04$ | 0.0270 | 0.0099 | $6.5 \mathrm{E}-03$ |
| Triglycerides | 0.0568 | 0.0070 | $3.6 \mathrm{E}-16$ | 0.0548 | 0.0149 | 6.1E-04 | 0.0581 | 0.0220 | 1.1E-02 | 8.37E-01 | 0.0460 | 0.0116 | 7.0E-05 | 0.0460 | 0.0188 | 1.5E-02 |
| BMI | 0.0260 | 0.0126 | $3.9 \mathrm{E}-02$ | 0.0068 | 0.0149 | 6.5E-01 | 0.0916 | 0.0313 | 4.2E-03 | $2.76 \mathrm{E}-03$ | 0.0093 | 0.0161 | $7.8 \mathrm{E}-01$ | 0.0286 | 0.0194 | $1.4 \mathrm{E}-01$ |
| \% Body fat | -0.0758 | 0.0440 | 8.5E-02 | -0.0661 | 0.0652 | 7.2E-01 | 0.2180 | 0.1532 | 9.0E-01 | 7.31E-02 | -0.1170 | 0.0477 | 5.7E-01 | -0.0753 | 0.0744 | 7.7E-01 |
| Waist hip ratio (adjusted by BMI) | 0.0391 | 0.0077 | 3.7E-07 | 0.0357 | 0.0106 | 8.8E-04 | 0.0936 | 0.0255 | 2.7E-04 | $1.28 \mathrm{E}-02$ | 0.0503 | 0.0122 | 3.6E-05 | 0.0321 | 0.0127 | 1.1E-02 |
| Fasting glucose | -0.0005 | 0.0004 | $1.7 \mathrm{E}-01$ | -0.0038 | 0.0370 | 9.2E-01 | -0.0074 | 0.0727 | 9.2E-01 | 9.54E-01 | -0.0143 | 0.0253 | 5.7E-01 | -0.0125 | 0.0274 | $6.5 \mathrm{E}-01$ |
| Fasting insulin | 0.0000 | 0.0006 | 9.9E-01 | -0.0810 | 0.1364 | 5.7E-01 | -0.8563 | 0.7542 | $2.9 \mathrm{E}-01$ | 3.21E-01 | -0.0415 | 0.0725 | 5.7E-01 | -0.0394 | 0.0844 | 6.4E-01 |
| T2D | 0.0010 | 0.0003 | $6.4 \mathrm{E}-04$ | 0.0176 | 0.0041 | $\begin{gathered} 5.53 \mathrm{f}- \\ 05 \end{gathered}$ | 0.0232 | 0.0082 | $6.5 \mathrm{E}-03$ | 4.4E-01 | 0.0233 | 0.0051 | 5.2E-06 | 0.0260 | 0.0063 | $\begin{gathered} 3.28 \mathrm{E}- \\ 05 \end{gathered}$ |



## CKDGen

| Trait | Beta grs | SE grs | P grs | Beta <br> IVW | SE IVW | P IVW | $\begin{aligned} & \text { Beta } \\ & \text { Egger } \end{aligned}$ | $\begin{aligned} & \text { SE } \\ & \text { Egger } \end{aligned}$ | P Egger | Egger <br> int $p$ | Beta <br> WM | SE WM | P WM | Beta PWM | SE PWM | P PWM |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Diastolic BP | Not available | Not available | Not available | 0.0136 | 0.0029 | 1.3E-05 | -0.0062 | 0.0082 | 4.5E-01 | $1.1 \mathrm{E}-02$ | 0.0143 | 0.0035 | 4.0E-05 | 0.0143 | 0.0035 | 5.6E-05 |
| Systolic BP | Not available | Not available | Not available | 0.0104 | 0.0019 | 3.7E-07 | -0.0043 | 0.0055 | 4.3E-01 | $5.5 \mathrm{E}-03$ | 0.0097 | 0.0022 | 1.1E-05 | 0.0098 | 0.0021 | 4.4E-06 |


| HDL cholesterol | Not available | Not available | Not available | -0.0098 | 0.0131 | 4.6E-01 | 0.0269 | 0.0175 | 1.3E-01 | 3.0E-03 | 0.0307 | 0.0161 | 5.7E-02 | 0.0307 | 0.0161 | 5.7E-02 |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| LDL cholesterol | Not available | Not available | Beta grs | SE grs | P grs | 2.4E-01 | -0.0262 | 0.0292 | 3.7E-01 | 4.3E-02 | 0.0029 | 0.0265 | 9.11-01 | 0.0253 | 0.0259 | 3.3E-01 |
| Triglycerides | Not available | Not available | Not available | 0.0697 | 0.0159 | 6.0E-05 | 0.0713 | 0.0231 | 3.4E-03 | 9.3E-01 | 0.0641 | 0.0212 | 2.5E-03 | 0.0641 | 0.0214 | 2.7E-03 |
| BMI | Not available | Not available | Not available | 0.0885 | 0.0292 | 3.4E-03 | 0.0662 | 0.0717 | 3.6E-01 | 3.9E-03 | 0.0559 | 0.0434 | 2.0E-01 | 0.0562 | 0.0434 | 2.0E-01 |
| \% Body fat | Not available | Not available | Not available | -0.2947 | 0.0804 | 2.9E-03 | -0.2399 | 0.2355 | 3.3E-01 | 8.0E-01 | -0.3053 | 0.1197 | 1.11-02 | -0.3053 | 0.1147 | 7.8E-03 |
| Waist hip ratio (adjusted by BMI) | Not available | Not available | Not available | 0.0651 | 0.0271 | 1.7E-02 | 0.1478 | 0.0805 | 6.8E-02 | 2.8E-01 | 0.0435 | 0.0398 | 2.7E-01 | 0.0305 | 0.0407 | 4.5E-01 |
| Fasting glucose | Not available | Not available | Not available | -0.0337 | 0.0499 | 5.1E-01 | -0.0921 | 0.0940 | 3.4E-01 | 4.7E-01 | -0.0321 | 0.0560 | 5.7E-01 | -0.0321 | 0.0551 | 5.6E-01 |
| Fasting insulin | Not available | Not available | Not available | 0.0561 | 0.1483 | 7.1E-01 | -1.8712 | 0.8257 | 4.3E-02 | 2.9E-02 | -0.0150 | 0.1282 | 9.11-01 | -0.0150 | 0.1287 | 9.1E-01 |
| T2D | Not available | Not available | Not available | -0.0133 | 0.0100 | 1.9E-01 | 0.0022 | 0.0216 | 9.2E-01 | 4.2E-01 | -0.0009 | 0.0164 | 9.5-01 | -0.0009 | 0.0164 | 9.5E-01 |




Standard deviation differences in ACR per standard deviation differences in genetically instrumented lipids measures.
No evidence of heterogeneity was noted between the MR estimates for the two different studies for HDL ( $p=0.844, \mathrm{l}$-square $0.0 \%$ ), LDL ( $p=0.788, \mathrm{l}$-square $0.0 \%$ ) and triglycerides ( $\mathrm{p}=0.494$, l-squared $0.0 \%$ ).


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