**The causal effect of adiposity measures on blood pressure traits in two urban Swedish cohorts: a Mendelian randomization study.**

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**Short Title:** The causal effect of adiposity on blood pressure

**Word Count: 5540**

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**Abstract**

**Background:** Different adiposity traits may be causally related to hypertension in different ways. By using genetic variants as randomly allocated proxies for studying the effect of modifying adiposity traits, the Mendelian randomization approach can be used to investigate this.

**Methods and results:** In this study, we used four different genetic risk scores (GRS-BMI565, GRS-WHR324, GRS-VAT208, GRS-BF81) including hundreds of single nucleotide polymorphisms associated with Body Mass Index (BMI), Waist to Hip Ratio (WHR), Visceral Adipose Tissue (VAT), and Body Fat (BF), respectively. These were applied as instrumental variables in Mendelian Randomization analyses. Two Swedish urban-based cohort studies, the Malmö Diet and Cancer and the Malmö Preventive Projects were used to obtain genetic association estimates with blood pressure (BP).

In both the Malmö Preventive Projects and Malmö Diet and Cancer, except for that for BF, all the GRSs were significantly associated with systolic BP and diastolic BP, but with different magnitudes. In particular, in both cohorts, each standard deviation increase in the GRS-WHR324 was associated withdoubling of the likelihood of hypertension prevalence at baseline. However, only the GRS-BMI565 was significantly associated with hypertension incidence during 23.6±4.3 years of follow-up in the Malmö Preventive Project.

**Conclusions**: We have supported a causal link between genetically mediated adiposity, especially WHR and BMI, and BP traits including hypertension prevalence and, for the first time to our knowledge, hypertension incidence. The differences in magnitude between these associations might suggest different mechanisms by which different adiposity affects BP/hypertension and consequently may indicate that tailored interventions are needed to reduce cardiovascular risk.

**Key words:** Mendelian randomization, blood pressure, adiposity, genetics, polymorphisms

Non-standard Abbreviations and Acronymous

2SLS: Two Step Least Square

BF: Body Fat

BIA: Bioelectrical Impedance Analyzers

BMI: Body Mass Index

BP: Blood Pressure

GRS: Genetic Risk Score

GRS-BF81: Genetic Risk Score made up by 84 SNPs associated to BF

GRS-BMI565: Genetic Risk Score made up by 565 SNPs associated to BMI

GRS-VAT208: Genetic Risk Score made up by 208 SNPs associated to VAT

GRS-WHR324: Genetic Risk Score made up by 324 SNPs associated to WHR

GWAS: Genome-Wide Association Studies

Il-6: Interleukin 6

IV: Instrumental Variable

IVW: Inverse Variance Weighted

MDC: Malmö Diet and Cancer

MPP: Malmö Preventive Project

MR: Mendelian Randomization

SNP: Single Nucleotide Polymorphism

TNF-α: Tumour Necrosis Factor-alpha

VAT: Visceral Adiposity Tissue

WHR: Waist to Hip Ratio

**Introduction**

Obesity and hypertension are two of the main causes of non-communicable diseases and mortality worldwide1,2. It is well-known that adiposity itself is a risk factor for hypertension 3 but how different measures of obesity influence blood pressure (BP) is less clear.

On one hand, genome-wide association studies have now pinpointed hundreds of genetic variants that are associated with not only Body Mass Index (BMI), but also with Waist-Hip Ratio (WHR), visceral fat mass and body mass distribution 4–7. On the other hand, Mendelian Randomization (MR) studies have supported that BMI and other adiposity measures are causally related with hypertension 8,9.

Adiposity is a complex trait, whose genetic component is influenced by the contribution of many different loci. From latest genome-wide association studies (GWASs), the number of genetic variants (single nucleotide polymorphisms; SNPs) found to be associated to different measures of body fat distribution has exponentially increased5,7. A genetic risk score (GRS), obtained by summing up weights and risk alleles of the SNPs associated to the trait, is a powerful tool to capture the genetic component of complex phenotypes10.

But, even if GRS obtained in large GWAS and meta-analyses were validated in very well-powered studies they need replication in other independent samples to assess the reproducibility of the genome-phenotype association11. The objective of a Mendelian randomization analysis is to test a causal hypothesis and the genetic information, that we used in form of GRS, represents the instrumental variable (IV) that is linked to the outcomes only through the endogenous variables (the adiposity measures) 12,13. Indeed, a MR design can reduce reverse causality and confounding.

The Malmö Diet and Cancer (MDC) and the Malmö Preventive Projects (MPP) are two large urban-based cohort studies based in Malmö in Southern Sweden in which >27,000 participants were genotyped. In the two samples, different measures of adiposity (BMI, waist circumference, hip, and body fat) as well as BP, were recorded. In the MPP there is also the possibility to evaluate hypertension incidence (not only prevalence) during follow-up, as this cohort was re-examined 23.6±4.3 years after the baseline exam.

Thus, the aim of the present study was to evaluate the association of different measures of genetically mediated adiposity with different BP-related traits including also hypertension prevalence and incidence, using a MR design.

**Methods**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Cohorts**

MDC

Cross-sectional BP, hypertension prevalence at baseline were studied in the MDC, a large-scale urban population-based cohort consisting of 30,447 individuals (58±7.6 yrs) from Malmö, Sweden. Of these, 29,386 were genotyped for GWAS. Men aged 46-73 and women aged 45-73 included between 1991 and 1996 were included.14,15

MPP

Hypertension prevalence and incidence were studied in the MPP, an urban-based prospective study with BP measurements available both at a baseline exam, including 33,346 citizens from Malmö (Sweden) between 1974 to 1992 and 18,240 at a re-examination between 2002 to 2006 .16 Of those, 9,367, who were included also in the MDC, underwent GWAS genotyping.

Characteristics of the two cohorts are presented in table S1

**Blood Pressure measurement**

In the MDC cohort at baseline, BP was measured manually once in the supine position after 5 minutes rest. To deal with the cofounding of the antihypertensive treatment on BP, we used a stepped addition method, in which 8/4, 14/10, 20/16, and 26/22 mmHg were added to SBP/DBP in presence of 1, 2 , 3 or 4 medications respectively17.

In the MPP cohort, at the baseline investigation, BP was measured after 1-minute rest in the supine position followed by another measurement after 1 minute in an upright standing position. This procedure was repeated also after 10 minutes of resting. For those subjects with a least three valid measurements, BP values were averaged and used for the analysis. At reinvestigation (after a mean follow-up time of 23.0±4.7 years), two measures in supine position were recorded. For those subjects with at least 2 valid measures, we used the averaged BP values. Both systolic (SBP) and diastolic (DBP) blood pressure were increased respectively, using a fixed addition adjustment method by 15mmHg and 10mmHg in presence of antihypertensive treatment17, since the number of medications was not available.

In both cohorts, Korotkoff sounds phase I was defined as SBP and phase V as DBP 18.

In both cohorts hypertension was defined as having either SBP or DBP greater than 140 mmHg or 90 mmHg; or taking antihypertensive drugs, in line with current European guidelines2. Hypertension prevalence could be evaluated in both the MDC and MPP cohorts at baseline, whereas in the MPP, also hypertension incidence at the re-investigation survey was investigated. For this analysis, individuals that were already hypertensive at baseline (n=3,135) were excluded.

**Adiposity measurements**

In both cohorts, height and weight were measured by trained nurses, as previously described19,20. BMI (kg/m2) was computed as weight divided by squared height. Waist circumference (cm) was measured between the lowest rib margin and the iliac crest and the hip circumference (cm) as the largest circumference between waist and thighs. Waist to hip ratio (WHR) was computed. In the MDC, the percentage of body fat (BF) was estimated with Bioelectrical Impedance Analyzers (BIA) according to manufactures’ algorithm (BIA 103, JRL systems, single-frequency analyzer, Detroit, USA) (Table S2).

**Mendelian Randomization**

**Instrumental variables**

A genetic risk score for BMI (GRS-BMI565), a GRS for WHR (GRS-WHR324), a GRS for predicted visceral adiposity (GRS-VAT208) and one for body fat distribution (GRS-BF81) were constructed including respectively 565, 324, 208 and 81 independent SNPs retrieved from the most recent meta-analyses5-7. The scores were weighted for the beta coefficients reported in the primary studies5-7. Information about the studies can be found in table S3.

The four GRS (GRS-BMI565, GRS-WHR324, GRS-VAT208, GRS-BF81) were used as instrumental variables (IVs) in the Mendelian Randomization analysis.

**Exposure**

The BMI was used as exposure trait for the GRS-BMI565, GRS-VAT208 in both MPP and MDC cohorts, since visceral adiposity (VAT) measure was not available in the two cohorts; and the WHR was used as exposure for GRS-WHR324. In the MPP, the BMI was used as exposure for GRS-BF81 instead of body fat, since that measure was not available.

In the MDC the percentage of body fat was used as exposure for GRS-BF81.

**Individual-level data**

For continuous outcome (SBP, DBP at baseline, and at reinvestigation) two steps least square (2SLS) regression was used to assess the causal association of the four GRSs. The 2SLS consists of two regression steps: in the first stage the exposure is regressed on the instrumental variable; in the second stage, the fitted values obtained from the first regression step are used as independent variables in the regression on the outcome 21.

For binary outcomes (hypertension prevalence and incidence) we used the analog of 2SLS consisting of two sequential regressions with the difference that the second step consists of logistic regression of the fitted values from the first step on the outcome21.

The exposure traits (BMI, WHR, BF) and the outcomes (SBP, DBP) have been used as standardized residuals resulting after adjustment for age, sex, age2, age\*sex.

**Sensitivity analysis**

When dealing with multiple instrumental variables, an alternative approach to the aggregation in a GRS is to use the estimates from each of the instrumental variables using summarized data analysis, as in a meta-analysis 22. With the increasing number of variants used in MR investigations, it is increasingly unlikely that all variants are valid IVs 23.

Inverse-variance weighted (IVW) method, MR-Egger, and weighted median were used as sensitivity analyses in the MDC cohort to assess the robustness of any casual finding of the multiple genetic variants involved in the construction of the four adiposity trait GRSs, to avoid IVs assumption 24. IVW is a weighted mean of the ratio estimates, and it is equal to estimates of 2SLS 22, it is liable to bias if only one IVs doesn’t satisfy IVs assumption and in presence of pleiotropy 23. The weighted median estimate is similar to IVW expect for the use of a weighted median instead of a weighted mean, and it is consisted up to 50% invalid instruments 23. The MR‐Egger allows to estimate the causal effect taking into account the Instrument Strength Independent of Direct Effect (InSIDE) assumption, which states that the pleiotropic associations of genetic variants must be uncorrelated with the genetic variant–exposure association23.

**Software**

All analysis was performed R software (R Core Team, 2019, packages *ivpack, MendelianRandomization*)25 and SPSS Software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

**Results**

**Association of IVs with the exposures**

In **Table 1** and **Figure 1** the association of each of the four GRSs used as instrumental variable (IV), with their related exposure traits, are presented. The contribution to model in terms of R-squared and the F statistic is also reported.

**Association to blood pressure traits**

In **table 2** the results from the Mendelian randomization analysis of the four adiposity GRSs with the continuous traits SBP/DBP at baseline are shown for MPP (part a.) and MDC (part b.). In the MPP (table S4, part a. and Figure 2), all the GRSs with the exception of the GRS-BF81 identify significant associations with baseline SBP and DBP. In the MDC (table S4, part b. and Figure 3) the associations with baseline measurements were in line with the results in the MPP. In both studies, the GRS-WHR324 shows the strongest association, in particular with DBP. At the MPP follow-up, only the GRS-BMI565 remains significantly associated to the BP-related traits (Figure 2b).

In tables 2, the associations of the four GRSs with the prevalence of hypertension is reported. A higher Odd Ratio is found with GRS-WHR324 as compared to other adiposity-GRSs for both MPP (Table 2 and figure 3a) and MDC (Table 2 and figure 3c).

Regarding hypertension incidence in MPP, after the exclusion of participants already hypertensive at baseline, only the GRS-BMI565 remained significantly associated to incident hypertension (Figure 3b).

Results from sensitivity analysis are presented in the Supplementary file (Table S8). As expected, the invariance weighted method (IVW), reflects the results obtained by the 2SLS regression of the GRSs on the traits (Table S4). The latter shows significance associations for all score with both traits except for the GRS-BF81. Among the four scores the only one that showed a significant MR Egger method is the GRS-WHR324 both for SBP and DBP (table S8 and figure S3-S6).

**DISCUSSION**

**Summary of main findings**

The main finding of the present study is that genetically proxied measures of adiposity, as condensed in specific GRSs, are associated with BP related traits but with different magnitude. In particular, the GRS-BMI565 and theGRS-WHR324 were potentially causally associated with all BP-related traits measured at baseline but the WHR had a higher estimate size. On the contrary, at follow-up, the genetically predicted association of WHR with BP tends to be attenuated and is no longer significant whereas that of BMI is still significant, although all the associations tended to be weaker than in the prevalence analysis. About more complex measures of adiposity such a body fat and visceral fat, their genetic component seems to be more limited in determining BP but still significant when hypertension prevalence is evaluated, at least in the MDC.

Even if some reasons for these discrepancies can stand on the relative weakness of the instrumental variables used with some GRS being stronger than others, it is likely that our study can give some clues to understand more deeply the biology of the well-known influence of body fat on BP. In fact, our data may indicate that the effect of BMI is important but with low magnitude throughout midlife to old age being recognizable in people in their forties and fifties (the average age in the MPP was 45±7.4 yrs and in the MDC is 58±7.6 yrs) but also in older ones (the average age in MPP at reinvestigation is 68±5.8 yrs). Instead, the contribution to high BP of genetically determined abdominal fat, represented by WHR, could seem much higher in midlife, overcoming the effect of BMI, than later on. However, an analysis done by stratifying participants by age in the MDC showed an inverse trend for the GRS-WHR324 with older individuals more strongly associated with prevalent hypertension than younger ones suggesting a possible survival bias for the analysis in MPP where participants with especially deleterious GRS-WHR324 could have died before the examination. (see also table S7 end figure S2).

**Explanation in the context of existing research**

Our results are in line with those of two recent studies but with some differences 8,9. In a MR analysis, including ~400,000 individuals from UKBiobank, a GRS-BMI resulted to be associated to BP (beta [95%CI]: 0.19 [0.18,0.21] for SBP and 0.27 [0.26,0.29] for DBP) and to hypertension prevalence (OR [95%CI]: 1.10 [1.07,1.12]) of the same order of magnitude of the results we found in the MDC 8. Also, the association of genetic component of body fat and VAT with hypertension, that we found in the MDC, is consistent with a previous MR performed in UK Biobank 6,9; despite we used BMI instead of VAT as exposure trait. Even if the association of the instrumental variable GRS-WHR with BP/hypertension is reported in a previous study8, the magnitude of the association is much higher in our samples.

A reason for such a difference in magnitude is not clear. Differences between the two samples in age (slightly lower in the UK-Biobank respect to the MDC), ethnicity (more homogeneous in the MDC), distribution of sex (higher prevalence of females in the MDC), and adiposity and BP traits (obesity is more prevalent in the UK-Biobank but hypertension in the MDC) can be postulated as a partial explanation.

The debate of which adiposity measure could better predict blood pressure or hypertension is still open, even in nongenetic studies. There are several pieces of research comparing BMI, waist, WHR, waist-to-height ratio (another proxy for central obesity), and VAT showing somewhat contradictory results. I.e. some studies, including a couple of meta-analyses, conclude that waist-to-height and waist circumference are stronger predictors than BMI of future CV events and hypertension. 26,27 But others 28–30 show that BMI is preferentially associated with the incidence of hypertension with respect to WHR. Then, a study in young adults (18-36 years) shows that BMI has an equal or better ability to predict adult hypertension as compared to WHR and other adiposity measures 31. Moreover, other well-powered analyses found that either VAT or BF are strongly associated with blood pressure traits 32 and the incidence of hypertension 33,34. One problem in this type of study is that the adiposity measures are highly correlated with each other and associate with differing levels of measurement error that could affect the strength of the observed associations 32. Mendelian Randomization could be considered an advantage in inferring causality since the usage of GRS is less susceptible to cofounding from environmental factors or reverse causation, respect to the raw trait measures.

**Possible mechanisms and clinical relevance**

Even if it is widely accepted that obesity and hypertension are interrelated and in particular the former is one of the causes of the latter, from a pathophysiological perspective, it has not been clarified how adiposity can influence BP at different ages. It is widely accepted that arterial stiffness is one of the main factors contributing to higher SBP in older ages. Other pathophysiological mechanisms potentially linking obesity to high BP refer to metabolic factors, endothelial and vascular dysfunction, the hyperactivation of the sympathetic nervous and the renin-angiotensin-aldosterone systems, sodium retention with a shift of the well-known pressure-natriuresis curve toward higher BP levels, and/or other renal dysfunctions 35,36. A pivotal player seems to be also the VAT that becomes resistant to insulin and leptin and is the site of altered secretion of molecules and hormones such as adiponectin, leptin, resistin, TNF-α and IL-6 37,38.

From the data of our study, it could be possible to speculate that adipokines especially produced in visceral fat and insulin resistance are more important for BP and the development of hypertension in midlife whereas total fat is important throughout life and still determinant when arterial stiffness become prominent.

In previous MR studies**,** BMI was also suggested to be causally associated with metabolic traits such as insulin and inflammation markers, such as IL-6 that could be on turn associated with hypertension development over time39.

Recently, it was shown that SNPs related to visceral adipose tissue (VAT) fat, i.e that found around abdominal organs, is strongly associated also with hypertension. In the same study, the heritability of VAT was found to be as high as more than 35%6; and the genetically determined VAT was associated with hypertension spanning between 1.81/1.89 in men/woman respectively for the rank-transformed VAT (that is the VAT after rank-transformation to standard normal distributions for females and males separately) to 2.17/3.41 for the bias corrected VAT (VAT corrected for measurement errors in a covariate-adjusted model). These results are fairly in line with the result in our study and quite similar to that of genetically determined WHR. The similar magnitude of the result for WHR and VAT underlines the pivotal role of visceral fat for high blood pressure.

**Strengths and limitations**

Among the strengths of this study, the use of the more recently validated GRSs associated with adiposity and the MR design that can preserve by issues of confounding and reverse causality; and the results were supported in sensitivity analyses that are more robust to the presence of variants with pleiotropic associations 40,41. Finally, to our knowledge this is the first study performing MR between adiposity traits and the incidence of hypertension, not only prevalence.

Our study has limitations. There is overlap between the MDC and MPP samples so that, even if the two studies had their own examinations at different time-points, the one cannot be considered a real replication of the other. Some GRSs used as instrumental variables were weaker than others, especially when proxy traits were used as exposure. Thus, some of the differences in the associations we found between adiposity-related GRSs and BP-related traits could be due to the fact that GRS-BMI565and GRS-WHR324 were better instrumental variables than GRS-BF81 and GRS-VAT208. In addition, GRS-BF81 and GRS-VAT208 were regressed on BMI in the MPP study, necessarily dampening their predictive value. Moreover, we have different statistical power for the different BP-related traits (i.e. hypertension incidence and prevalence). In addition, the hypertension incidence outcome, apart from the diminished sample size, could be blurred by the fact that the analysis is restricted to people less prone to develop hypertension (i.e. the ones that have not developed hypertension at baseline).

Finally, there is possible presence of pleiotropy among the studied variants. Indeed, a clear dissection between all the observed adiposity-related traits is not possible and several SNPs, especially those encompassed in loci that have previously been associated with obesity and BMI, such as the well-known *FTO* and *MC4R* loci, are common between the different GRSs. All the above-mentioned points, that in some ways could be considered intrinsic limitation of the usage of genetic variants as instrumental variable 42, contribute to reduce the strength of the causal inference of our analysis. Indeed, any causal inference drawn from MR analyses alone should be considered tentative.

**Conclusion**

In conclusion, we have demonstrated that genetically predicted adiposity, and especially genetically predicted WHR and BMI, are potentially causally linked to BP and hypertension. Tailored interventions to block this deleterious relationship should be pursued and in particular intervention to decrease waist circumference and BMI throughout life are likely to be most effective.

**Source of Funding**

Lund University Infrastructure grant” Malmö population-based cohorts” (STYR 2019/2046).

Dipender Gill is supported by the British Heart Foundation Centre of Research Excellence (RE/18/4/34215) at Imperial College London and a National Institute for Health Research Clinical Lectureship at St. George's, University of London (CL-2020-16-001).

**Disclosure**

Dipender Gill is employed part-time by Novo Nordisk, outside of the submitted work.

**Supplemental material: Regeneron Genetics Center Banner Author List and Contribution Statements, Supplementary Tables 1-8; Supplementary Figure 1-6**

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**Tables**

Table 1 Association of the four GRSs (expressed as per one SD increment) with their related exposure traits (expressed as SD) at baseline in the MPP and MDC cohorts.

|  |  |  |
| --- | --- | --- |
|  | **MPP** | **MDC** |
|  | **Beta (95%CI)** | **p-value** | **R2** | **F** | **Beta (95%CI)** | **p-value** | **R2** | **F** |
|  | **BMI** | **BMI** |
| **GRS-BMI565** | 0.201 (0.179,0.218) | 8.0E-86 | 0.005 | 393 | 0.200 (0.189,0.211) | 3.4E-263 | 0.04 | 1,226 |
|  | **WHR** | **WHR** |  |
| **GRS-WHR324** | 0.086 (0.065,0.107) | 4.8E-16 | 0.007 | 66 | 0.046 (0.034,0.057) | 4.7E-15 | 0.002 | 61 |
|  | **BMI** | **% bodyfat** |  |
| **GRS-BF81** | 0.063 (0.043,0.083) | 9.5E-10 | 0.004 | 37 | 0.045 (0.034,0.057) | 1.5E-14 | 0.002 | 59 |
|  | **BMI** | **BMI** |  |
| **GRS-VAT208** | 0.128 (0.107,0.147) | 1.19E-35 | 0.016 | 156 | 0.136 (0.125,0.147) | 1.12E-121 | 0.02 | 555 |

Legend: BF, Body Fat; BMI, Body Mass Index; F, F statistics; GRS-VAT208, Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; GRS-BF81, Genetic risk score for Body Fat based on 81 SNPs; GRS-WHR324 Genetic Risk Score for Waist Hip Ratio based on 324 SNPs; GRS-BMI565, Genetic Risk Score for Body Mass Index based on 565 SNPs; MPP, Malmö Preventive Project; MDC, Malmö Diet and Cancer; R2, r-squared; WHR, Waist Hip Ratio.

Table 2 Association of the four adiposity GRSs (expressed as SD increase) with hypertension prevalence in the MPP

|  |  |  |  |
| --- | --- | --- | --- |
|  | Hypertension Prevalencen=9,137 | Hypertension Incidencen=5,971 | Hypertension Prevalencen=29,262 |
|  | Model 1 |  | Model 2 |  | Model 1 |  | Model 2 |  | Model 1 |  | Model 2 |  |
|  | OR (95%CI) | p-value | OR (95%CI) | p-value | OR (95%CI) | p-value | OR (95%CI) | p-value | OR (95%CI) | p-value | OR (95%CI) | p-value |
| GRS-BMI565 | 1.51 (1.21, 1.88) | 0.0003 | 1.48 (1.19,1.83) | 0.0003 | 1.34 (1.03,1.74) | 0.029 | 1.33(1.03,1.72) | 0.03 | 1.70 (1.50,1.93) | 1.1E-16 | 1.56 (1.39, 1.75) | 8.5E-14 |
| GRS-WHR324 | 2.46 (1.46,4.14) | 0.001 | 1.85 (1.33,2.58) | 0.0003 | 1.07 (0.58,1.98) | 0.820 | 1.05 (0.70,1.57) | 0.820 | 3.81 (2.28,6.37) | 3.5E-7 | 2.95 (1.95,4.47) | 3.5E-7 |
| GRS-BF81 | 1.46 (0.71,2.99) | 0.274 | 1.45 (0.74,2.83) | 0.274 | 0.48 (0.21,1.11) | 0.079 | 0.49 (0.22,1.09) | 0.079 | 1.12 (1.03,1.21) | 0.006 | 1.57 (1.08,2.28) | 0.02 |
| GRS-VAT208 | 2.01 (1.43,2.83) | 6.2E-5 | 1.95 (1.41,2.70) | 6.2E-5 | 1.28 (0.85,1.94) | 0.235 | 1.27 (0.86,1.89) | 0.235 | 1.61 (1.35-1.91) | 7.6E-8 | 1.59 (1.34,1.88) | 7.6E-8 |

Legend:GRS-VAT208, Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; GRS-BF81, Genetic risk score for Body Fat based on 81 SNPs; GRS-WHR324 Genetic Risk Score for Waist Hip Ratio based on 324 SNPs; GRS-BMI565, Genetic Risk Score for Body Mass Index based on 565 SNPs; BMI, Body Mass Index; BF, Body Fat; WHR, Waist Hip Ratio. Model 1: raw association (without adjustment); Model 2: the exposure trait was used as the residual from linear regression with age, sex, age2,age\*sex.

**Figures**

Figure 1 Causal association from 2SLS MR between the GRSs and BP traits, in the MPP cohort

Figure 2. Causal association from 2SLS MR between the GRSs and BP traits, in the MDC cohort

Figure 3. Forest plot of the association of the four GRSs with the prevalence of hypertension at baseline in the two cohorts and with the incidence of hypertension at follow-up in the MPP cohort

**Legends**

Figure 1

Legend: DBP, diastolic blood pressure; GRS-VAT208, Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; GRS-BF81, Genetic risk score for Body Fat based on 81 SNPs; GRS-WHR324 Genetic Risk Score for Waist Hip Ratio based on 324 SNPs; GRS-BMI565, Genetic Risk Score for Body Mass Index based on 565 SNPs; SBP, systolic blood pressure.

Each Forest plot shows the causal estimates (β) from the 2SLS regression of the four GRSs

with baseline (a.) and follow-up (b.) blood pressure outcomes (SBP or DBP) in the MPP cohort for the model 2 (adjustment for age, sex, age2, age\*sex). I.e. an increase of 1 SD in GRS-VAT208 is associated with an SD increase of 0.326 of SBP.

Figure 2

Legend: DBP, diastolic blood pressure; GRS-VAT208, Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; GRS-BF81, Genetic risk score for Body Fat based on 81 SNPs; GRS-WHR324 Genetic Risk Score for Waist Hip Ratio based on 324 SNPs; GRS-BMI565, Genetic Risk Score for Body Mass Index based on 565 SNPs; SBP, systolic blood pressure.

Each Forest plot shows the causal estimates (β) from the 2SLS regression of the four GRSs with blood pressure outcomes (SBP or DBP) in the MDC cohort for model 2 (adjustment for age, sex, age2, age\*sex). I.e. an increase of 1 SD in GRS-VAT208 is associated with an SD increase of 0.236 of SBP.

Figure 3

Legend: GRS-VAT208, Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; GRS-BF81, Genetic risk score for Body Fat based on 81 SNPs; GRS-WHR324 Genetic Risk Score for Waist Hip Ratio based on 324 SNPs; GRS-BMI565, Genetic Risk Score for Body Mass Index based on 565 SNPs; OR, Odds ratio.

Each Forest plot shows the causal estimates in odds ratio, from the 2-stage logistic regression of the four GRSs with the prevalence of hypertension at baseline in the MDC (a.) and the MPP (b.) and with the incidence of hypertension at follow-up in the MPP cohort (c.) for the model 2 (adjusted for age, sex, age2, age\*sex). I.e. the increase of 1 SD in GRS-VAT208 is associated with an OR of 2.01 for hypertension prevalence.