A pipeline for Mendelian randomization studies using large metabolomics data as intermediates

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Abstract

This is where the abstract will go when you've done some actual work. . . ..

Acknowledgements

ALSPAC

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

The following ALSPAC identifiers are associated with the work in the associated chapters:

- Chapter 4: B3473, B3160, B3230

Data

I would like to thank Emma Anderson for providing the diet trajectory data used in this analysis.

Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

Signed

Dated

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Chapter 1

Introduction

Increased adiposity and associations with disease

This chapter provides the context of the thesis. It briefly gives the background on the problem of increased adiposity, the biology of adipose tissue, and diseases linking increased body mass index and mortality. The chapter briefly explores different measures of increased adiposity and potential hypotheses for underlying aetiology of diseases associated with increased adiposity. Finally, the potential application of metabolites and Mendelian randomization in the context of understanding underlying aetiology are discussed.

1.1 Background

Globally, the prevalence of overweight (body mass index (BMI) of 25–29.9 kg/m^2) and obesity (BMI > 30 kg/m^2) is 39% and 13% respectively[1](Figure 1.1 and 1.2). Obesity is estimated to be responsible for 8% of global deaths[2] and this number is likely to rise as the prevalence of obesity increases[3–5].

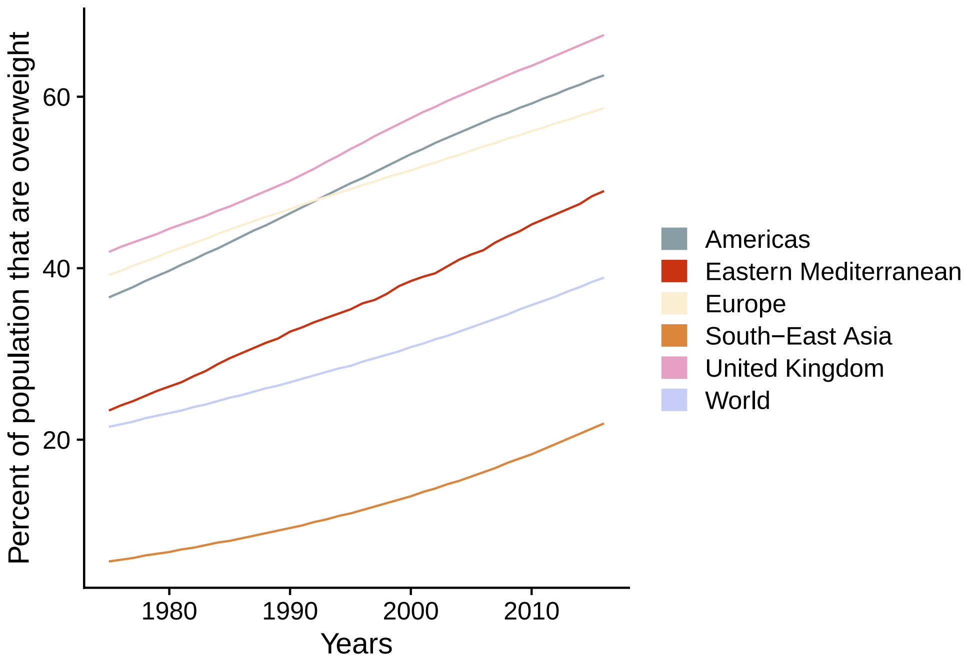

Figure 1.1: Proportion of overweight individuals

Figure 1.1 shows the share of adults (18+) that are overweight globally and in selected geographic regions including the United Kingdom from 1975 to 2016. Data from Ritchie and Roser (2019)[6]

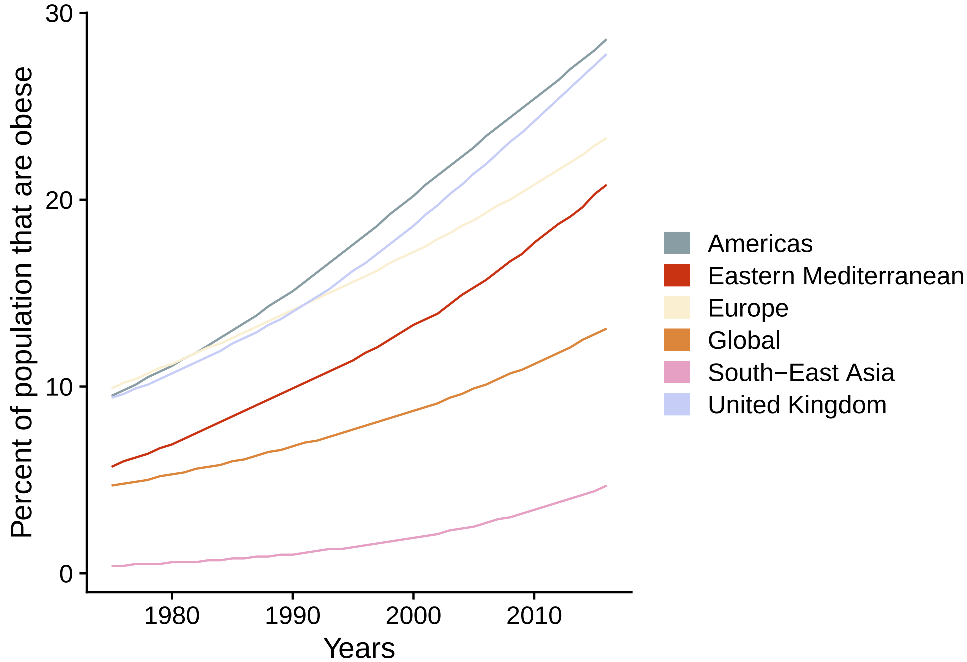

Figure 1.2: Proportion of obese individuals

Figure 1.2 shows the share of adults (18+) that are obese globally and in selected geographic regions including the United Kingdom from 1975 to 2016. Data from Ritchie and Roser (2019)[6]

Body mass index is a measure of weight given an adjustment of height and thus an approximation of body composition. Given its simplicity, BMI is the most commonly used measure of increased adiposity. Body mass index can be classified into sub-types according to the range of values seen in the general population. Whilst ethnicity, sex, and age specific, the international standards set by the WHO[7,8] estimate a normal weight classification at a population level to be a BMI of 18.5–24.9 kg/m^2, with an underweight class below this. Underweight is a specific condition that may be secondary to or symptomatic of an underlying disease and is not within the scope of this thesis.

1.2 Additional measures of increased adiposity

Though a simple and effective measure of increased adiposity, BMI does not have the resolution to accurately measure body composition[9–12]. This fact was discussed when first proposed and is particualrly evident in athletic and tall individuals[13].

There are also questions around the relationship with morbidity and mortality[14–16]. Though these questions are likely a result of confounding and other biases[17–19], evidence has pointed to a more important role for fat deposition in the relationship with mortality[20,21].

Complimentary assessment of increased adiposity, using a combination of body composition measures, may provide additional information into the associations with disease[22,23]. Alongside BMI, waist hip ratio (WHR) is frequently used to gain a better understanding of fat deposition. A WHR > 0.85 in in women and > 0.9 in men is considered equivalent to a BMI of > $30kg/m^{224}$. However, given that ultimately it is excess adipose accumulation that is responsible for disease development, direct assessment of body fat has been argued as key in understanding disease development[13]. Body fat percent (BF) provides an easily comparabile measure of excess adispose tissue.

Both WHR and BF are used clinically and for population-based research to provide more alternative measures of an individuals body composition. Whereas BMI provides an overall approximation of an individuals proportions, WHR provides an approximate assessment of the deposition of fat around the body; deposition of fat at the waist is indicative of greater visceral fat[22]. BF by its nature of measuring fat mass directly rather than estimating it like BMI, provides a more accurate estimation of body composition[25]. Both BMI and WHR have a single measurement while BF can be measured in a a number of different ways including estimations based on WHR and BMI. Imaging measures, such as dual-emission X-ray absorptiometry (DXA), enable direct measurement of adipose tissue and are the most accurate measure of BF though are not practical at scale.

As with BMI there are a number of considerations when using WHR and BF. Firstly, sexual dimoprhism is acutely present with both measures. Physiologically, women generally have more body fat than men for any given weight and/or height. This difference is observed after puberty. Fat deposition in women is predominantly around the hips while in men it is around the waist. This difference is refelected in their respective WHRs and is reason for the different threshold for obesity classification.

With both WHR and BF there is potential for measurement error. There are specific guidelines produced by the WHO for taking waist and hip circumference measurements[24] and it is estimated that error can be as high as $1.56cm$[24]. Measurement error for BF is dependent on the method used. For all methods the fasted status of the individual and whether they had recently performed exercise can influence measurement. Impedance devices aim to measure resistance of an electric current passed through an individual, with resistance, age, height, weight, and sex used in proprietary equations. As these equations are commercially sensitive their application to different populations is difficult to appraise. However, studies have shown similar results with more accurate measures of BF[26,27]. Though imaging studies are able to directly measure fat-free and fat mass, a hard call must still be made as to whether the measured area is coded as fat-free or fat mass. That being said, there is high interindividual reproducibility of DXA measures[28].

Like BMI[14–16], WHR[9,29–32] and BF[29,32–34] are also associated with mortality. Performing a manual literature search for WHR and the categories identified in the MELODI analysis (Table A.1) reveals a number of associations including: cancer[35], cardiovascular[36,37], kidney[38], liver[39], neurological/behavioural[40,41], pregnancy[42], respiratory[43] and diabetes[44]. For BF, fewer studies were reported in the literature with associations including: cancer[33], cardiovascular[33,45], kidney[46], respiratory[33], and diabetes[47].

1.3 Adipose tissue

Weight is made up of two components, fat free mass and fat mass. Fat free mass encompasses muscle, bone and water mass. Fat mass is an all encompassing term for adipose tissue. Adipose tissue is predominantly made up of adipocytes, with other tissues and cells such as the stromal vascular fraction, preadipocytes and fibroblasts making up smaller proportions[48–50]. The main function of adipose tissue is energy storage in the form of lipids, with a secondary function to insulate the body and maintain thermoregulation. These two functions can broadly be separated into two types of adipose tissue, white and brown[49].

In addition to energy storage and insulation, adipose tissue is considered an endocrine organ, responsive to afferent signalling as well as being a prolific signaller itself[51]. Advances in genetics and availability of large population studies has enabled the identification of single nucleotide polymorphisms (SNPs) and genes associated with increased adipose tissue[52].

1.3.1 Energy storage

Energy storage is determined by energy intake and energy expenditure. An increase or decrease in one leads to a change in energy balance and thus an increase or decrease in total energy storage as $Energy\ balance = energy\ in - energy\ out$. Energy stores are comprised primarily of proteins, carbohydrates, and fats. For protein, there is little change in total energy stores outside of a growth stimulus (i.e. exercise is needed to increase protein stores)[53]. Carbohydrate stores fluctuate markedly throughout the day as a result of limited storage capacity and the fact that they comprise the majority of energy production[53]. Fats are the largest energy store. Daily fat intake is ~1% of the total available fat store[53]. Given the tight controls over protein and limited availability of carbohydrate storage, fat storage is the only expandable reservoir of excess energy intake[48,53]. As a result, an energy imbalance will be reflected in the fat stores and not elsewhere[48,53].

Excess energy is stored in adipocytes in the form of lipid droplets (triglycerides; Figure 1.3) via lipogenesis. The release of these fat stores, in the form of fatty acids, occurs through lipolysis. As the main store of excess energy, triglycerides provide an accurate reflection of energy imbalance, while adipocytes reflect the deposition and mobilisation of triglycerides[48]. Deposition and mobilisation of triglycerides, depicted in Figure 1.3, is a product of a complex interplay of genetic and hormonal signals with leptin and insulin playing key roles[54]. Insulin stimulates the conversion of acetyl-CoA to triglycerides by encouraging uptake of glucose by adipocytes and promoting production of SREBP1 (sterol regulatory element-binding protein 1). SREBP1 regulates fatty acid, triglyceride and cholesterol synthesis[48,50]. In addition, lipoprotein lipase plays a key role in hydrolysing circulating triglycerides into fatty acids enabling their uptake by adipocytes[48]. Though they can expand, individual adipocytes have limited storage capacity for triglycerides. Once *full*, adipocytes have the ability to multiply[48]. The amount of expansion adipocytes can achieve is limited[48,55] and thought to be influential in the rate of adipogenesis, the rate of fat mobilisation around the body and the development of disease[55].

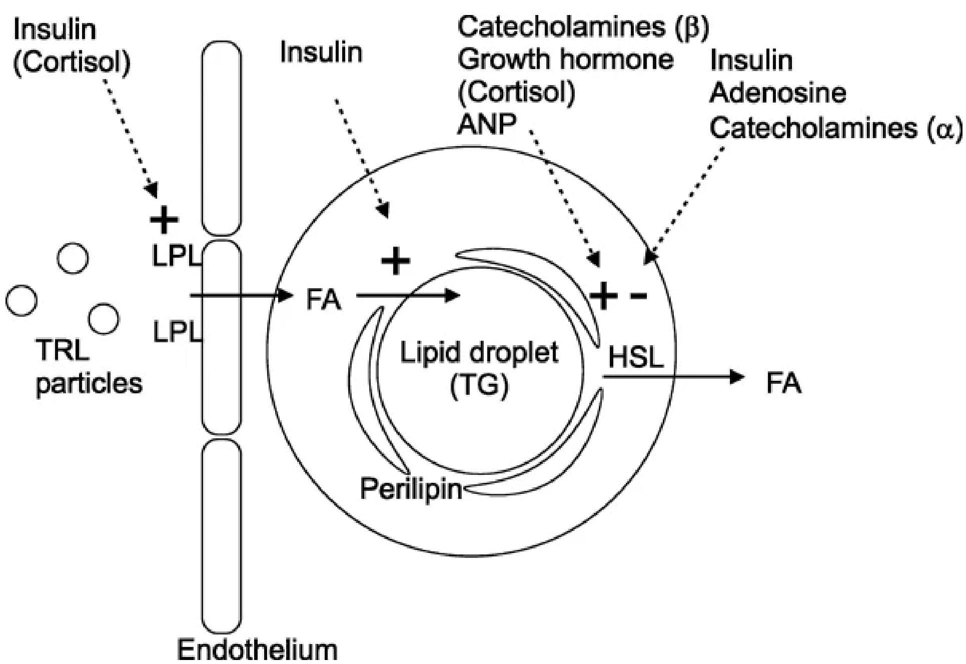

Figure 1.3: Diagram of adipocyte fat deposition and mobilisation

Figure 1.3, reproduced from Frayn et al. (2003)[48], depicts influences on adipocytes that result in fat storage. Stimuli such as insulin result in positive (+) fat deposition, while other stimuli such as cortisol may result in positive or negative (-) fat deposition depending on *the location of the adipocyte within the body. ANP, atrial natriuretic peptide, FA, fatty acids; LPL, lipoprotein lipase; TG, triglyceride; TRL, TG-rich lipoproteins.*

1.3.2 Insulation

Energy storage of fats is managed predominantly by white adipose tissue. These deposits are located mainly within subcutaneous tissue. During infancy, brown adipose tissue is abundant; however, as humans age these deposits *whiten* leaving few adult brown fat deposits. The remaining deposits of brown adipose tissue in adults are located around the neck, thoracic section of the spine, aortic body, and adrenal glands; all locations with high blood flow[50,56]. Thermogenesis by these tissues is regulated by the hypothalamus and is achieved by uncoupling of the respiratory chain of oxidative phosphorylation via UCP1 (uncoupling protein 1). When this process is active, lipids and glucose are used as fuel[56]. Due to the abundant vascularization of areas where brown adipose tissue is located the heat generated from this process is quickly distributed via the circulatory system. In addition, white adipose tissue can undergo a *beiging* process taking on thermogenic properties of brown adipose tissue. Beige adipose tissue is a half way point between white and brown adipose tissue and is more widely dispersed than brown adipose tissue, being located mainly within subcutaneous white adipose tissue. Beige adipose tissue, much like brown adipose tissue, is cold activated but can be recruited through signalling that mimics the stressed state induced by cold. The *beiging* process is not well characterized but is thought to be a result of signalling changes during differentiation of preadipocytes[50]. The *beiging* process is reversible but has been suggested as a therapeutic avenue for weight loss[56].

1.3.3 Signalling

It is important to consider adipose tissue as an organ in its own right. Not solely comprised of adipocytes, adipose tissue includes a multitude of tissues and cells including connective and nerve tissues and immune cells. All respond to, and secrete, signalling molecules locally and systemically. It is thought this signalling is primarily to maintain appropriate energy stores and includes signals influencing deposition and mobilisation of fats and differentiation of new adipocytes[48,50,51]. Functionally, signalling molecules have metabolic effects and/or are involved in steroid hormone production[51].

Adipogenesis, the process of adipocyte formation, has been well characterized and PPARy (peroxisome proliferator-activated receptor y) is the master regulator[48,50]. Over-expression of PPARy leads to differentiation and under-expression results in lipodystrophy. Other signalling molecules such as KLFs (Kruppel-like factors) and C/EBPs (CCAAT-enhancer-binding proteins) influence adipogenesis through PPARy[50]. Because of the master regulatory function of PPARy, exploring regulatory function and expression has been considered as a potential therapeutic avenue for obesity[50,57]. Though not well characterized, brown adipocytes are thought be influenced heavily by PRDM16 and PGC1a, with the latter required for thermogenesis and not necessarily adipogenesis[50]. The breakdown of stored triglycerides via lipolysis results in the release of fatty acids and glycerol molecules for oxidation and gluconeogenesis respectively. Fatty acids can also be broken down into ketone bodies via ketogenesis. While insulin abundance activates lipogenesis, the relative absence of insulin promotes lipogenesis. The lipolytic pathway, which is also activated by cAMP-dependent (cyclic adenosine monophosphate) PKA (protein kinase A), relies on the function of ATGL (adipocyte triglyceride lipase) and HSL (hormone sensitive lipase) to catalyse the hydrolysis of triglycerides to di- and mono-glyceride's respectively. Inhibition of ATGL can result in impaired lipolysis and obesity[58].

The signalling molecules adipocytes produce, known as adipokines, are numerous and act on the auto- and endo-crine systems[59,60]. There are adipose deposit specific effects on expression and secretion of adipokines and the movement these adipokines can be expected to undertake. Subcutaneous adipose tissue adipokines travel through the systemic system while visceral adipose tissue adipokines can travel via the portal system with direct access to the liver. Adipocyte receptors are also expressed differentially based on deposit location[51]. The main adipokines (Figure 1.4) produced by adipocytes are leptin and adiponectin which function to regulate metabolism and inflammation systemically. Other cells within the adipose tissue, including immune and endothelial cells, produce much of the other adipokines such as TNFa (tumour necrosis factor a) and IL6 (interleukin 6)[50].

Abnormal levels of adipokines are harmful, as they lead to impaired adipose tissue function and subsequent downstream effects such as insulin resistance[50,60–62]. As adipose tissue abundance increases so too does the likelihood of abnormal levels of adipokines. This is of particular interest as adipokine levels can change as a result of diseases such as obesity, thus introducing feed-back loops which serve to alter normal processes[60,61]. However, there are outstanding questions about how abnormal levels of adipokines leads to the development of disease[60]. For detailed discussion of adipokines and the pathways that lead to their production, which is not in the scope of this thesis, see[50,51,60–62].

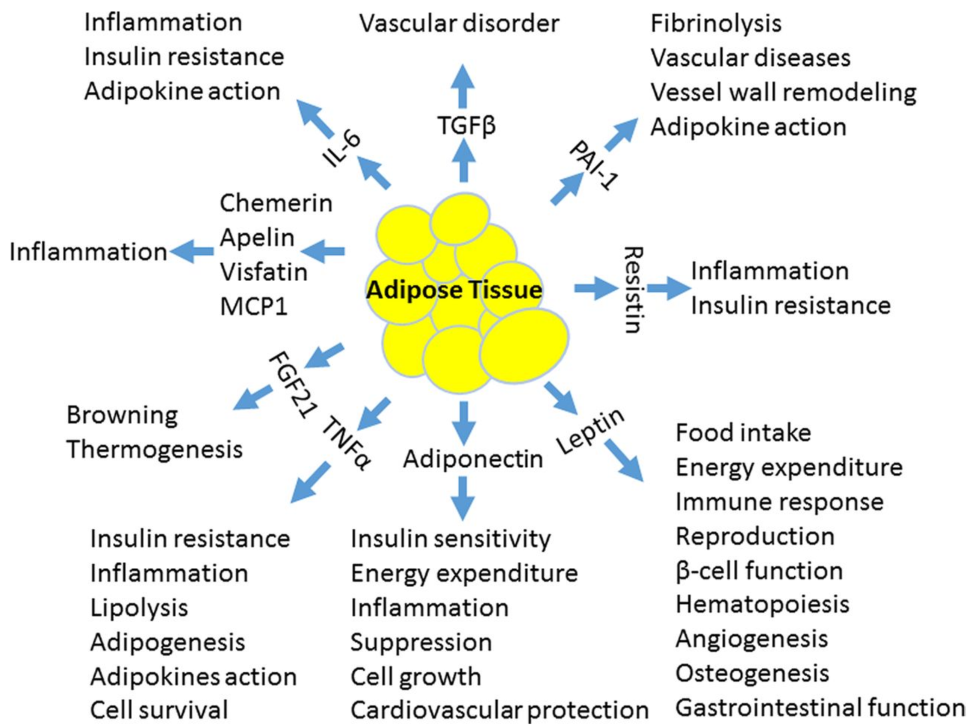

Figure 1.4: Diagram of the main adipokines secreted by adipose tiusse

Figure 1.4, reproduced from Luo and Liu (2016)[50], shows the main adipokines secreted by adipose tissue and their local and systemic functions. ASP, acylating simulation protein; FGF21, fibroblast growth factor 21; IL6, interleukin 6; MCP1, monocyte chemoattractant protein 1; PAI1, plasminogen activator inhibitor 1; TNFα, tumour necrosis factor alpha.

1.3.4 Genetics

Production of adipokines, though partly a response of afferent signalling, is also a result of adipocyte genetics. This is also the case for lipogenesis, storage capacity, lipolysis, mobilisation of fat deposits and energy expenditure[52]. A number of adipose specific genes have been identified including *LEP*[63,64], *ADIPOQ*[65], and *PPARy*[64,66] encoding the adipokines leptin and adiponectin and the adipose-specific transcription factor PPARy. These, and other genes[64], are expressed differently in subcutaneous and visceral adipose tissue as well as in non-adipose tissue[64]. Differential expression along with the presence of adipose-specific genes is associated with obesity and related diseases[64]. For example, *SLC19A3* is an adipose-specific gene[64] encoding a thiamine transporter; thiamine dependent enzymes have been associated with obesity[67]. As adipocyte expandability is limited, and given that an excess of fatty acids results in increased adipogenesis[48,55], it is possible that expandability is fixed by adipose-specific genes and expression. This may have an impact on the development of diseases such as type-2 diabetes where incidence differs between different ancestral populations with the same BMI[68].

1.4 Body mass index and disease

With obesity responsible for 8% of premature deaths per-year[2] and more people expected to be overweight or obese in the coming years[3–5] it is important to understand how increased adiposity leads to mortality. Large scaleliterature searching (see Supplementary @ref(#chapter1-appendix)) highlights the broad array of diseases and complications linking BMI and mortality. These diseases and complications can broadly be categorised as: Cancer, Cardiovascular, immune, Kidney, Liver, Neurological/behavioural, Other, Pregnancy, Respiratory, where *other* includes disease like diabetes and the metabolic syndrome (Table A.1).

1.5 Underlying aetiology of the BMI disease relationship

Although associated with many of the same diseases, the underlying aetiology of the relationships between BMI, WHR and BF with these diseases is not clear. For quality of life, the relationship is mostly explained by the presence of co-morbidities which increases the likelihood of poor outcomes. Stigmatisation as a result of increased fat mass may also be involved in poor quality of life[69,70]. Similarly, the relationship with many sleep complications is likely a result of chronic pulmonary diseases – distribution of fat mass around the neck may also be important[69–71].

Type 2 diabete development is likely to follow a process of impaired glucose clearance as a result of increased adiposity, which leads to increased insulin resistance. There are likely wider metabolic changes that influence this process which are also a consequence of increased adiposity[23,69,70]. Respiratory diseases are likely a result of reductions in FEV1, FVC, lung and residual capacity, and expiratory reserve. Each of these is a consequence of weakened muscles and reduced compliance of the chest which can be caused by the physical burden of increased adiposity around the chest and lungs[70,71]. With respiratory disease there is also the prospect of confounding as a result of smoking status, which increases with increased adiposity[72]. In the case of cardiovascular disease, hypertension may be related to changes in: sympathetic activity, blood flow and viscosity, and dietary intake as a result of increased adiposity[69,70,73]. Some of these changes might similarly be a result of metabolic, inflammatory and hormonal changes. Both dyslipidemia and reductions in HDL result from increased adiposity and these changes may be important in development of heart disease.

Unlike diabetes and respiratory diseases, most other diseases have a less well understood process of development as a result of increased adiposity. Increased adiposity is associated with numerous types of cancer. Hypotheses for these associations differ based on the type of cancer. Metabolic, inflammatory and hormonal changes as a result of increased adiposity are proposed as leading to the development of a number of different cancers[23,69,70,74].

The location of fat deposits may also be important (e.g. deposition of adipose tissue around the heart may result in inflammation of the myocardium, but this might also be subsequent to dyslipidemia and reduction in HDL[23,69,70,75]). Osteoarthritis, though likely a result of the physical burden of increased adiposity, may also be a product of changes to cartilage and bone metabolism[69,70]. Similar metabolic changes may play a role in a number of other diseases. An increased risk of gallstones is associated with increased cholesterol[69] and increased salt intake has been suggested as a potential link between increased adiposity and stroke[23,70].

The body of work investigating associations between increased adiposity and disease is extensive. Many proposed mechanisms of disease development invovle the physical burden of fat mass and/or changes to different pathways, particularly metabolic changes. However, the potential for residual confounding and reverse causation in these studies warrants further investigation using methods robust to there challenges.

1.6 Mendelian randomization

Studies investigating the associations between increased adiposity and metabolites and metabolites and disease are important and, when conducted in optimal conditions provide information on the potential causes and consequences of altered metabolic states. Even with optimal conditions observational studies hold a number of limitations that can not easily be overcome. These limitations, such as confounding and reverse causation, can lead to biased results[76–79]. Simply put, though a study may identify an association between two traits does not mean that one causes the other; they may be correlated because of shared causes for instance.

In observational epidemiology, ideally we want to compare individuals based on the exposure and so attempt to control the experiment by accounting for confounderis. In this regard we attempt to replicate a randomised control trial, wich is the gold standard for testing causality. However, the large costs and time required to develop, implement and analyse results limits their use. More importantly, randomizing individuals to conditions known to be associated with harmful outcomes is ethically wrong. An alternative approach is to utilise the large amounts of data that are publicly available or that can be accessed through institutions. Causal inference methodologies have been established to exploit the availability of these data sets.

Mendelian randomization (MR), described[80,80,81] and reviewed[82,83] elsewhere, and accompanied by a dictionary of terms[84], is a statistical methodology that uses genetic variants as instrumental variables to investigate the causal relationship between an exposure and outcome[80,85]. The reassessment of many observational associations has provided strong evidence for the relationships between risk factors and diseases, but has also highlighted the biases and limitations of observational research[77–79].

Briefly, individuals inherit alleles largely at random from their mother and father. Across a large population this leads to the even distribution of confounders between the effect and non-effect alleles. As such, individuals differ because of the expressed allele rather than their environmental circumstances. This random allocation of genetic variants, which may ultimately be related to a health outcome, is analogous to a randomised control trial where geneotype groups act as the intervention and non-intervention arms of the trial.

Inference derived from MR analyses relies up-on three assumptions (Figure 1.5): (i) the instrumental variable (Z) is robustly associated with the exposure (X), (ii) there is no independent association of the instrumental variable with the outcome (Y) other than through the exposure, (iii) the instrumental variable is independent of measured or un-measured confounders (U).

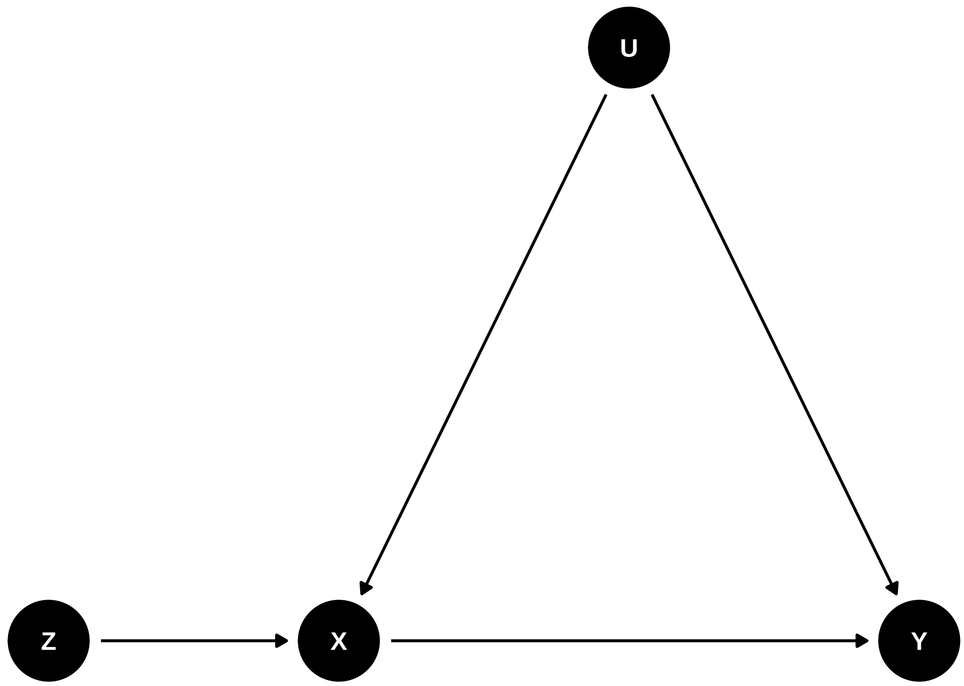

Figure 1.5: Directed acyclic graph of the Mendelian randomization principle

Z = instrumental variable; X = exposure; Y = outcome; U = confounders.

Additional assumptons based on homogeneity, monotonicity, and effect modification are also present. The homogeneity assumption assumes the assoication between the IV and the is exposure or the effect of the exposure on the outcome is homogeneous. That is, the association or the effect is the same for all individuals in the population. Monotonicity can be deterministic or stochastic. Deterministic monotonicity assumes that the effect of the IV is consistent in all individuals of the population. That is, the effect of the IV does not increase the exposure in one group and decrease it in another. Stochastic monotonicity assumes deterministic monotonicity conditional on confounders.

Based up-on Mendel's laws of inheritance, MR relies on the assumption that genetic variants are unlikely to be associated with one another (outside of linkage disequilibrium) or with environmental factors. Deviation from which would mean an uneven distribution of alleles across a population. Consideration in MR analyses should therefore also be given to dynastic effects, population structure, and assortative mating. Within family MR can be used to obtain the true causal effect in these situations[86,87].

Dynastic effects, a form of confounding, are a consequence of traits transmitted across generations which then influence the causal effect estimate[87,88]. That is, the parental genotype directly effects the offspring phenotype. For example, the effect BMI on cardiovascular disease may be biased by the instrumental variables for BMI being correlated across parent and offspring and the effect of maternal BMI on offspring development, which has an effect on future cardiovascular disease. In this instance the seond MR assumption would be violated. Within family studies are proposed, and simulations have shown, to overcome some of the consequences of dynastci effects[87,88].

Population structure is a result of allele frequency differning across geographic regions. This would violate the assumption that instrumental variables are independent of confounding factors. In MR analyses it is assumed that latent structure is accounted for in the genome-wide association study (GWAS) in which the instrumental variables are discovered[89]. As the sample sizes of GWAS's has increased the potential for subtle effects of population structure has been observed[89,90].

Assortative mating is the principle by which partners select one another based on a particular phenotype. This is either cross-trait (one trait selecting for another trait) or single-trait (one trait selecting for the same trait). MR results can be biased by both types of assortative mating, even when the phenotypes of interest are not those which influenced the mating[86].

Canalization, whereby what would otherwise be developmentally deleterious genetic effects are nullified by compensatory mechanisms, is broadly equivalent to non-adherence in an RCT. Any effects of canalization would attenuate effect sizes[85], however there are currently no methods to detect its presence in an MR context. The effects of canalization are unlikely to be present in MR studies which utilise maternal genotypes for environmental exposures of the offspring such as during gestation[91]. For complex traits it is possible that canalization occurs at the level of the system rather than at the gene level[92]. As such, any outcome of a genetic mutation in regards to its role in the canal would likely be unpredictable.

Methodological advances have enabled MR studies to be conducted with both individual level, known as one-sample MR, and summary level data obtained from published GWASs[93], known as two-sample MR. In both contexts, instrumental variables are often obtained from external GWAS's. Increasingly, these are large and well powered GWAS' able to idnetify ever increasing numbers of SNPs assocciatied with complex traits such as with BMI[94–98]. As power has increased, the ability to detect SNPs with smaller effects and which explain ever smaller proportions of variance in BMI has increased[98]. This holds potential considerations in regards to population structure and the effects of an omnigenic model.

As discussed, population structure was thought to have been an issue in smaller studies and could be accounted for by adjustment. However, well powered studies have shown both latent structure[89,90] and an inability to perform adequate adjustemnt[99]. This has potential implications, not only for the effect sizes of associated SNPs but also for the identification of SNPs associated with the trait[99]. For example, a poorly or un-adjusted GWAS could identify SNPs associated with population differences rather than the trait of interest.

In an omnigenic model, variance in a trait of interest is not solely a result of directly related genes (core-genes). Rather, all genes expressed in relevant cell types have an effect, however small, on the trait of interest[100]. These peripheral-genes, which have no obvious direct link to the trait of interest, are mostly in non-coding regions with regulatory functions[101].Given that variants associated with complex traits are dispersed widely across the genome[101] and that assigning a link between any particular SNP and an individual gene is difficult[102], variants associated with complex traits likely implicate many genes with the trait. Because many of these will be peripheral-genes they will ultimately have functions on other traits, which in an MR context may include the outcome and thus violate the exclusion restriction assumption.

Additional considerations include random measurement error (random measurmeent in the exposure will bias towards the null, and increase the standard error if in the outcome), Winners curse (whereby discovery studies identify larger effects than those in replication studies), collider bias (conditioning on a variable by adjustment, restriction, or sampling can induce an association betwene X and Y biasing th estimate both away and towards the null), non-overlapping samples (specific to two-sample MR, where the exposure and outcome data are obtained from samples with shared individuals), horizontal pleiotropy (the instrumental variable has an affect on the outcome independent of the exposure), and vertical pleiotropy (the instrumental variable does not have an effect on the exposure directly but on traits that have an effect on the exposure).

Among the considerations and limitations of MR, population stratification, horizontal pleiotropy and canalization are the most challenging to account for. Though one can restrict analyses to homogeneous groups, use principal components, and perform within family studies to examine and mitigate the effects of population stratification, biases (e.g. sampling bias) may still remain. Additionally, methods for assessing potential horizontal pleiotropy exist but formal assessment of the exclusion restriction assumption is not possible. Accounting for canalization is much harder and, though being aware of the underlying biology can inform ones analyses, methods for assessment do not exist. Unlike the other considerations, vertical pleiotropy does not necessarily bias MR results rather it highlights potential intermediates.

Both one-sample and two-sample MR can be extended to investigate intermediates that sit on the causal pathway. Mediation analysis in MR is discussed in detail elsewhere[103] and can be achieved using two-step[104]/network MR[105] and multivariable MR[106] (MVMR). Briefly, mediation analysis is interested in identifying the total effetc, the direct effect, and the indirect effect; where all act in the same direction the proportion of the total effect explained by teh mediator (proportion mediated) can be calculated[107]. The total effect is the effect of the exposure on the outcome through all mediated pathways, the direct effect is the effect of the exposure on the outcome through all mediated pathways that are not the pathway of interest, the indirect effect is the effect of the exposure on the outcome through the mediator of interest. These analyses are predicated on the following assumptions: (i) that there is a causal effect of the exposure on the outcome and mediator and of the mediator on the outcome; (ii) that there is no confounding between exposure, mediator, and outcome; (iii) that there are no intermediate confounders; (iv) that there is no interaction between the exposure and mediator[107].

In two-step MR (Figure 1.6) the indirect effect is calculated by multiplying the effect of the exposure on the mediator and the effect of the mediator on the outcome. The three core MR assumptions (and all previous considerations) must still be met and also extended: (i) the instrumental variables (Z & $Z2$) must be robustly associated with the exposure or intermediate only (X and M), (ii) the instrumental variables for the exposure (Z) must not be associated with the intermediate (M) or the outcome (Z) other than through the exposure (X), and the intermediate instrumental variables ($Z2$) must not be associated with the exposure, and only with the outcome (Y) through the intermediate, (iii) the instrumental variables for the exposure and intermediate must not be associated with measured or unmeasured confounders. No interaction between exposure and mediator is also assumed. Two-step MR has been used[108–110] and combined with MVMR[111] to gain better insight into disease aetiology.

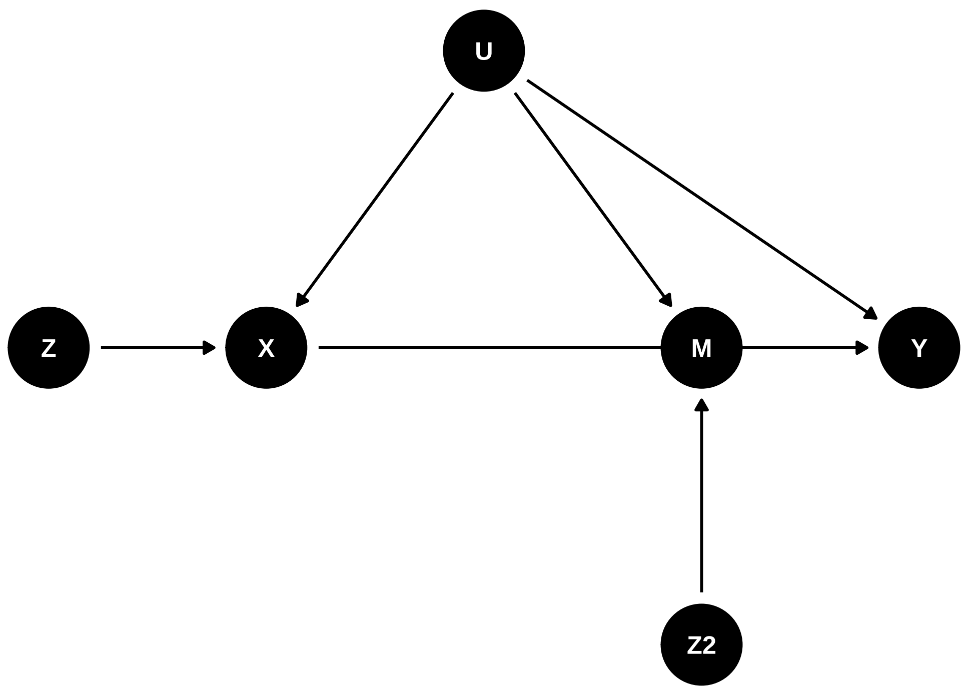

Figure 1.6: Directed acyclic graph of the two-step Mendelian randomization principle

Z = instrumental variable; X = exposure; M = intermediate; U = confounders; $Z2$ = instrumental variable for M; Y = outcome.

Multivariable MR allows for the causal effects of multiple exposures on an outcome to be estimated[106] (Figure 1.7). The effect of each exposure is estimated conditional on the other exposures and thus provides a direct estimate of the effect. Figure 1.7 shows a simplified MVMR model with two exposures (X and $X2$); the bidirectional line between exposure one and exposure two does not make an assumption about the exposure relationships. The indirect effect is estimated by subtraction of the direct effect from the total effect. The total effect is calculated using univariable MR. As with two-step MR, no interaction between exposure and mediator is assumed. Though a new approach, and still subject to the same assuptions as with two-step and univariable MR, MVMR has shown promise in elucidating underlying aetiology of complex traits[111–114].

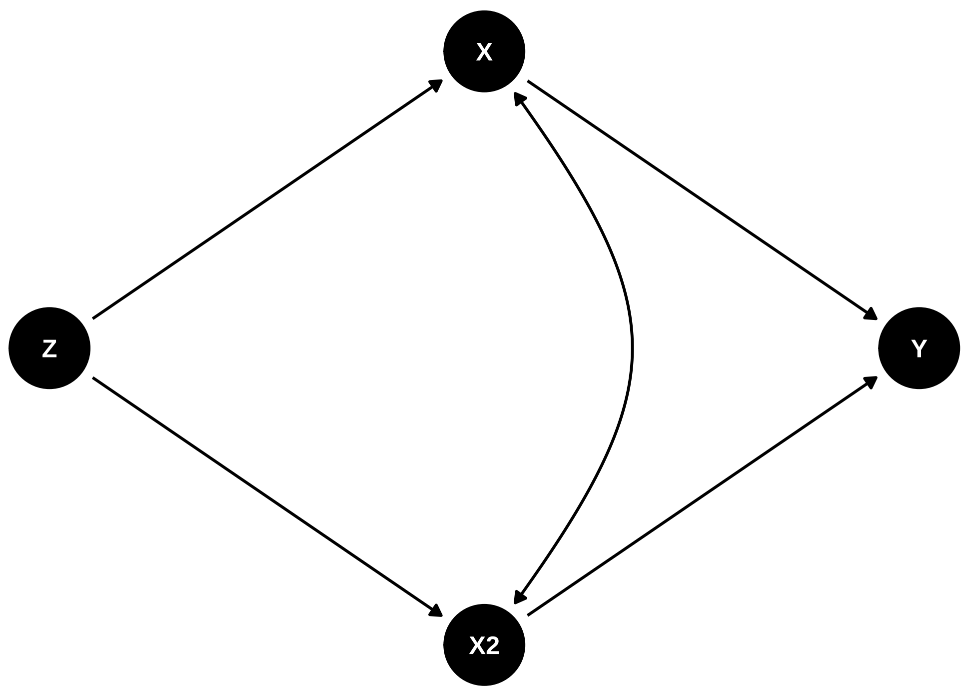

Figure 1.7: Directed acyclic graph of the multivariable Mendelian randomization principle using two exposures

Z = *instrumental variables associated with one or more of the exposures;* X = *exposure;* $X2$ = *second exposure;* Y = *outcome.*

Though two-step MR was devised with epigenetic mechanisms in mind[104] and MVMR has shown promise investigating metabolic intermediates[113], their application to large omic data sets is yet to be shown. An alternative approach, which insted of estimating mediated effects looks for overlapping signals, may also be appropriate for omic data[NOTE: INSERT REF TO RCC PAPER]. In this regard, the effect of the exposure on the candidate intermediate and the effect of candidate intermediate on the outcome are ranked in terms of their effects. A candidate intermediate is considered to be a potential mediator if it ranks highly in both analyses. [NOTE: DISUCSS LIMITATIONS ONCE PAPER IS COMPLETED]

1.7 Metabolites

Many of the diseases discussed (Section 1.5) have hypothesised development processes involving metabolic, inflammatory and hormonal changes. As a complex signalling organ with both local and systemic effects, adipose tissue is likely to influence all three of these processes at both local and systemic levels. It is not within the scope of this thesis to investigate all three, but recent advances in measurement methodologies and the availability of large, and deeply phenotyped population based studies may now provide the data necessary to investigate metabolic effects.

The metabolome, the total abundance of small-molecules, is a reflection of genetic and non-genetic factors and sits between the proteome and the phenotype[115–118]. The metabolome can be separated into endogenous (internally produced) and exogneous (externally produced) metabolites, whereby the majority of metabolites are the result of cellular processes, with multiple functions including as energy, signalling, transportattion, and structural components. Metabolic effects can be far reaching and also include post-translational modifications[118,119]. During homeostasis metabolic effects are tightly controlled, however the many functions they play mean that imbalances can be detrimental[115,118,119].

Measurement of individual metabolites, at scale, is achieved predominantly through mass spectrometry (MS) and nuclear magnetic resonance (NMR). Both MS and NMR have differing limitations with full coverage of the metabolome not achieved by either. Complimentary usage of the two methods is desirable[120]; however, as MS is destructive and both methods are costly this is not always possible. Many population-based studies have metabolomics data from only one measurement method limiting the number of metabolites available for analysis.

The number, and type, of metabolites identified by MS and NMR methods is dependent upon whether a targeted, semi-targeted, or un-targeted approach is taken. Targeted metabolomics analysis uses an internal standard to characterize individual metabolites[121,122] whereas un-targeted metabolomics analysis measures all metabolites within a specified range[122,123]. Semi-targeted approaches use internal standards to quantify groups of metabolites with similar chemical structure[122]. Targeted studies are able to identify a handful of metabolites where as semi-targeted and un-targeted can identify hundreds to thousands. As targeted and semi-targeted methods use internal standards absolute quantification of metabolit abundance is possible. In un-targeted methods only relative quantification, the peak area of each metabolite in comparison to other samples, is possible[122].

The availability of well powered population studies with metabolomics data from targeted, semi-targeted, and un-targeted methods as well as matched genome-wide data has enabled a growth in metaboloite GWASs[117,120]. These studies have revealed large variations in the heritability of metabolites and numerous loci associated with their abundances[124; 125; 126; 127; Lotta2020]. The public availability of these GWASs provides a unique opportunity to perform genetic epidemiology studies which can compliment the existing literature from observational association studies.

Metabolites reflect the current condition and activity of an organism and vary in abundance depending on the state of the individual. This is particularly evident in fasted and non-fasted measurements[128–130] but also in case control studies such as those focussing on diabetes[131] and cancer[119,132]. Differences are also apparent when studying complex traits such as BMI[133,134] as well as many more[135] - a searchable database of metabolite information, including links with disease, is available from The Human Metabolome Database.

These studies provide an overall assessment of the changes metabolites undergo as a result of different conditions but the relationship is not clear. Whether metabolites change as a result of a condition or lead to its development is an important question with potential clinical importance. Mutable, both from a genetic and non-genetic perspective, the metabolome can, with caution, be used to investigate the development of diseases[116,117,120]. Particular consideration should be given to the metabolomics approach (targeted, semi-targeted, untargeted) and whether individuals were fasted. Consideration should also be given to the fact that metabolomics analysis provides a snapshot of an individuals current state. Though few studies have investigated metabolomic stability in large populations, variability in metabolite measures is apparent[128,136,137].

A key aspect of future work investigating relationships between metabolites and diseases are the interactions metabolites have with one another. The metabolome is a complex system involving feedback and feed-forward loops, this complexity means many metabolites are intercorrelated[138], have high genetic correlation[127] and share a common genetic architecture[124–127,139]. As such, a perturbation in a single metabolite rarely occurs in isolation. Investigating metabolites as grouped entities that represent the underlying complexity, rather than individual metabolites, may help to elucidate relationships with disease.

1.8 Aims

Increased adiposity is a global health concern. Many of the consequence of increased adiposity are known but the underlying aetiology is not well understood. Adipose tissue is a prolific signalling organ with systemic effects some of which are likely to affect the metabolome. Individual metabolites have been associated with many diseases but the complexity of the network makes these analyses difficult. MR studies provide an opportunity to investigate and disentangle the complex relationship between exposure, intermediate and outcome. These studies must be approached carefully given the interrelatedness of metabolites. In light of these considerations this thesis aims to:

- *Identify metabolites that sit on the causal pathway from increased adiposity to disease*

1.8.1 Objectives

In order to achieve this aim this thesis will investigate the following objectives:

1. Perform a systematic review (Chapter 2) of all MR studies in which a measure of increased adiposity was used as an exposure. The diseases identified in this work will guide the diseases investigated (Chapter 9).

2. Identify and describe appropriate instrumentation of increased adiposity. The systematic review (Chapter 2) will provide information on current instrumentation practices for MR. I will use this information and test MR

instrument assumptions using individual level data to select instruments for subsequent analyses (Chapters 3 and 4).

3. Identify metabolites associated with increased adiposity in observational (Chapter 4) and MR settings (Chapter 5).

4. Gain overview of metabolic profiles to enable interpretation of analyses from Chapters 4, 5, and 9 using visualisation tools (Chapter 6).

4. Implement methods to reduce the complexity of the metabolome and produce instruments for MR analyses (Chapters 7 and 8).

5. Identify diseases associated with metabolites in an MR setting (Chapter 9) and present the investigated network of increased adiposity -> metabolites -> diseases.

1.9 Summary

Within this chapter I have...... [NOTE: look to kaitlins thesis for an idea of how to link chapters together]

1.10 Presentation of results

In this thesis large association analyses are conducted. The presentation and interpretation of this data is complicated by the highly inter-correlated nature of metabolomics data and the need to compare effects across multiple exposures, models and ages. To this effect, and discussed in detail in Chapter 6, Circos plots have been used to visualise results. To aid interpretation of these going forward, and unless otherwise stated in the figure legend, the following applies:

- Each point represents a single test of an exposure on an outcome
- Labels around the edge of the plot represent outcomes
- Tracks represent a single variable (e.g. an exposure)
- Each point is accompanied by a 95% confidence interval
- Solid points represent a multiple testing threshold has been reached
- Data is split into sections (denoted by numbers) which is dictated by grouping outcomes by a variable (e.g. subclass)

Chapter 2

Systematic review

TITLE OF CHAPTER

Chapter 3

Instrumentation

Instrumenting measures of increased adiposity

Although the prevailing thought is that BMI, WHR, and BF% are all highly correlated there is little recent evidence from studies investigating all three measures simultaneously in the same populations. Evidence mainly comes from a study by Pouliot et al. (1994)[140]; for men they found corrleatins of: BMI and BF% = 0.85, BMI and WHR = 0.78, WHR and BF% = 0.70; women: BMI and BF% = 0.96, BMI and WHR = 0.58, WHR and BF% = 0.55. See Chapter 3

Given the high correlation between BMI, WHR, and BF% (at least sex specifically in the case of WHR and BF% - See Chapter 3) it may be likely that a study reporting an association between BMI and a disease will also show a similar association with WHR and/or BF%. We looked for review articles for BMI and multiple diseases and looked for studies reporting BMI and WHR and/or BF% to identify if studies found similar associations across multiple measures of increased adipsoity. Table **??** shows studies identifying an association between BMI and a disease and studies which show similar associations with WHR and BF%. A summary of the studies which discuss underlying aetiology of the associations is also presented.

As a result, we first set out to investigate the correlation between BMI, WHR, and BF% in two independent population based studies: the Avon Longitudinal Study of Parents and Children[141,142](ALSPAC) and UK Biobank[143–145].

3.0.1 Correlation of measures of increased adiposity

Data

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a large prospective cohort study that recruited 14,541 pregnancies in the former Avon Health Authority area in South West England, with expected delivery dates between the 1st April 1991 and the 31st December 1992[141,142] (See Supplementary Information, ALSPAC Overview, for full details). We used data from the Focus clinics for mothers and fathers. We used the clinic with the highest response rate for each of mothers and fathers, this was clinic 1 for both. For Focus on Mothers 1 (FOM1) data was collected between December 2008 and July 2011 with a total of 4,832 women attending clinic. Because mother may have enrolled multiple pregnancies the total number of cases in the release data is 4,978 mothers; the mean age of the mothers was 47.89 (4.497 SD). For Focus on Fathers 1 (FOF1) data was collected between September 2001 and February 2013 and a total of 2,001 fathers attended the clinic. Multiple pregnanices resulted in a total number of cases in the release data as 2,034; the mean age of fathers was 53.3 (5.427 SD). Prior to data analysis we removed duplicate cases of mothers and fathers using `R`[146](version 3.5.3) resulting in 4,831 and 2,001 women and men for analysis.

In FOM1 and FOF1 BMI was derived from `weight (kg) / height (m^2^)`; WHR was derived from `wasit circumference (cm) / hip circumference (cm)`; BF% was obtained from a full-body scan using a narrow fan beam dual-emission X-ray absorptiometry (DXA; Lunar Prodigy) scanner and derived from `total fat mass / (total fat free mass + total fat mass) * 100`. Data was avaliable on 4,632 women and 1,826 men (Table 3.1).

UK Biobank is a prospective study of ~500,000 individuals aged 37-79 recruited from 2006-2010 who were registered with the Natonal Health Service in the United Kingdom and lived close to one of 22 assessment centres. Participants provided a range of information at a single assessment (See Supplementary Information, UK Biobank Overview)[143–145]. We used the final release of data () which included information on XXX women and XXX men. Before analysis we removed all individuals. . . . . . this resulted in XXX and XXX women and men for analysis.

In UK Biobank BMI was derived from `weight (kg) / height (m^2^)`; WHR was derived from `wasit circumference (cm) / hip circumference (cm)`; BF% was obtained . . . . Data was avaliable on 4,632 women and 1,826 men (Table 3.1).

Table 3.1: Study characteristics for measures of increased adiposity in ALSPAC and UK Biobank.

	ALSPAC	UK Biobank

	Women	Men	Women	Men
BMI	4810	1976	1	1
WHR	4809	1985	2	2
BF%	4649	1839	3	3
Total	4632	1826	4	4

Table 3.1 shows the number of individuals from the Avon Longitudinal Study of Parents and Children (ALSPAC) and UK Biobank with available data for each measure of increased adiposity after removing individuals with missing data for each trait. Total shows the number of individuals with a measure for all three measures of increased adiposity; we performed correlation analysis on this group. BMI = body mass idnex; WHR = waist hip ratio; BF% = body fat percent; Total = the number of individuals for each category with inforation on all three measures and after exclusions.

Statistical analysis

To investigate the correlation between BMI, WHR, and BF% we performed a Pearson's product-moment correlation in R[146](version 3.5.3) for each of ALSPAC women, men, sex combined, and UK Biobank women, men, and sex combined. All results are reported in Table 3.2 and shown in Figure 3.1 and **??**.

Table 3.2: Correlation results for measures of increased adiposity in ALSPAC and UK Biobank.

	Women	Men	Combined

	R	CI	R	CI	R	CI
ALSPAC						
BMI & WHR	0.48	0.46 – 0.50	0.63	0.60 – 0.66	0.42	0.40 – 0.44
BMI & BF%	0.81	0.80 – 0.82	0.77	0.75 – 0.79	0.65	0.63 – 0.66
WHR & BF%	0.36	0.33 – 0.38	0.65	0.63 – 0.68	-0.09	-0.06 – -0.11
UK Biobank						
BMI & WHR	1.00	1	1.00	1	1.00	1
BMI & BF%	2.00	2	2.00	2	2.00	2
WHR & BF%	3.00	3	3.00	3	3.00	3

Table 3.2 shows the Pearson's product-moment correlation estimates (R) and associated 95% confidence interval (CI) for each combination of BMI, WHR, and BF% seperated by sex and data source. Combined = sex combined analysis; ALSPAC = Avon Longitudinal Study of Parents and Children; R = Pearson's product-moment correaltion estimate; CI = 95% confidence interval for the correlation estimate. All correlation results reporte a p-value < 2.2 x 10^{-16} except for: ALSPAC sex combined WHR & BF% (p-value = 5.197 x 10^{-12}),. . . . .

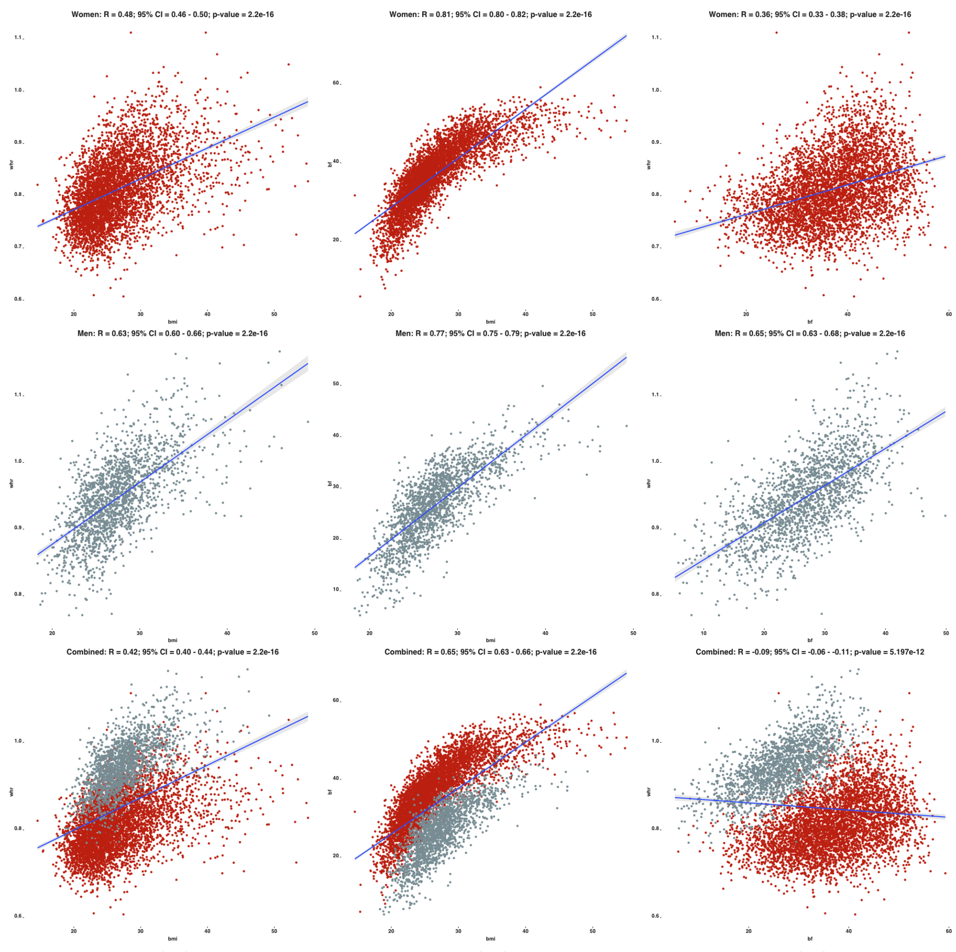

Figure 3.1: Scater plots of ALSPAC individuals data on measures of increased adiposity

Figure 3.1 shows scatter plots for ALSPAC women (top), men (middle) and combined (bottom) data on BMI and WHR (left), BMI and BF% (centre), and WHR and BF% (right). A linear model line with 95% confidence interval is shown along with the Pearson's product-moment correalation (R) and associated 95% confidence intervals (95% CI) and p-values at the top of each scatter. BMI = body mass *idnex; WHR = waist hip ratio; BF% = body fat percent. All correlation results report a p-value < 2.2 x 10^{-16} except for ALSPAC sex combined WHR & BF% (p-value = 5.197 x 10^{-12}).*

Figure **??** *shows scatter plots for UK Biobank women (top), men (middle) and combined (bottom) data on BMI and WHR (left), BMI and BF% (centre), and WHR and BF% (right). A linear model line with 95% confidence interval is shown along with the Pearson's product-moment correalation (R) and associated 95% confidence intervals (95% CI) and p-values at the top of each scatter. BMI = body mass idnex; WHR = waist hip ratio; BF% = body fat percent. All correlation results report a p-value. . . . .*

In ALSPAC our results show the highest correlations between BMI and BF% for both men (95% CI = 0.75 – 0.79) and women (95% CI = 0.80 – 0.82), with similarly high correaltion for sex combined (95% CI = 0.63 – 0.66).

Our measure of DXA derived measure of BF% in ALSPAC is likely a more accurate quantification of BF% than Pouliot et al. (1994)[140] who derived BF% using hydrostatic weighing and an estimation equation[147]. Differences in estimates from ALSPAC and Pouliot et al. (1994)[140] may also be a result of sample sizes with only 70 women and 81 men in Pouliot et al. (1994)[140], with 66 and 22.5 times more women and men available for analysis in ALSPAC.

For UK Biobank correlation estimates are. . . . .

ALSPAC men women combined BMI and WHR = 0.60-0.66 0.46-0.50 0.40-0.44 BMI and BF% = 0.75-0.79 0.80-0.82 0.63-0.66 WHR and BF% = 0.63-0.68

0.33-0.38 -0.06- -0.11

UK Biobank men women combined BMI and WHR = BMI and BF% = WHR and BF% =

Pouliot et al. (1994)[140] men women BMI and BF% = 0.85 0.96 BMI and WHR = 0.78 0.58 WHR and BF% = 0.70 0.55

3.1 Supplementary Information

3.1.1 ALSPAC Overview

Pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992 were invited to take part in the study. The initial number of pregnancies enrolled is 14,541 (for these at least one questionnaire has been returned or a "Children in Focus" clinic had been attended by 19/07/99). Of these initial pregnancies, there was a total of 14,676 foetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 24 is 913 (456, 262 and 195 recruited during Phases II, III and IV respectively), resulting in an additional

913 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper and its update (see footnote 4 below). The total sample size for analyses using any data collected after the age of seven is therefore 15,454 pregnancies, resulting in 15,589 foetuses. Of these 14,901 were alive at 1 year of age. A 10% sample of the ALSPAC cohort, known as the Children in Focus (CiF) group, attended clinics at the University of Bristol at various time intervals between 4 to 61 months of age. The CiF group were chosen at random from the last 6 months of ALSPAC births (1432 families attended at least one clinic). Excluded were those mothers who had moved out of the area or were lost to follow-up, and those partaking in another study of infant development in Avon.

The study website `http://www.bristol.ac.uk/alspac/` contains details of all the data that is available through a fully searchable data dictionary and variable search tool `http://www.bristol.ac.uk/alspac/researchers/our-data/`. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees `http://www.bristol.ac.uk/alspac/researchers/research-ethics/`. Informed consent for the use of data collected via questionnaire and clinics was obtained from participants following recommendations of the ALSPAC Ethics and Law Committee at the time. Full details of the ALSPAC consent procedures are available on the study website `http://www.bristol.ac.uk/alspac/researchers/research-ethics/`.

3.1.2 UK Biobank Overview

This research has been conducted using the UK Biobank Resource under *Application Number 16391*.

Chapter 4

Observational analysis

Associations between measures of adiposity and metabolites: observational analysis

In Chapters 1 and 2, the link between increased adiposity and disease was presented both in observational and causal analysis frameworks. This work highlighted key limiting areas in understanding the biological pathways leading to disease development. In this chapter, observational epidemiological methods will be used to assess one of the potential pathways linking adiposity to disease, metabolites. The aim of this chapter is to provide an observational grounding for subsequent causal analysis work in Chapters 5 and 9.

4.1 Introduction

In Chapter 1 and 2, a growing body of work both observational and causal was presented linking increased adiposity to many diseases. Many of these, and others, have proposed metabolites to be involved in this process[23,69,70]. However, few studies have identified intermediate metabolites and pathways that lie on the disease development pathway.

Metabolic changes as a result of increased adiposity have recently been highlighted in a systematic review[148]. The studies included reveal the wide scale metabolic change as a result of obesity. However, the majority of studies included fewer than 100 individuals and all focused on obesity as a singular measure of adiposity.

Analysis across thousands of individuals has highlighted the wide range of global effects BMI has on the metabolome[149]. To our knowledge, the work by Wurtz et al. (2014)[149] is the largest investigation of the effects of increased adiposity on the metabolome to date. Their analysis, involving 88 metabolites measured in 12,664 adolescents and young adults, identified a majority of metabolites to be associated with increased BMI after adjusting for sex. Associations were observed across numerous metabolic classes including amino acids, fatty acids, hormones, inflammatory markers, and lipids. Amino acids were positively associated with BMI, with the largest effect observed for phenylalanine. Fatty acids showed similarly positive effects, except for n-6 fatty acids percentage and polyunsaturated fatty acids percentage which showed negative associations. A positive association was observed for LDL metabolites while a heterogeneous pattern of association was found for HDL metabolites. In MR analysis, similar results were found.

Given the crude estimation of adiposity provided by BMI, the effects identified by Wurtz et al. (2014)[149] require further consideration across a number of measures of adiposity. The Avon Longitudinal Study of Parents and Children (ALSPAC), a longitudinal birth cohort study, provides an opportunity to expand on this work using data from many thousands of individuals with multiple measures of adiposity and metabolomics data measured at multiple time points. Here, observational analysis of measures of adiposity and metabolites provide a basis from which to investigate causal associations. In addition, replication of results from Wurtz et al.[149] is possible for a number of metabolites.

4.2 Methods

Data were available for exposures (measures of adiposity), outcomes (metabolites), and potential confounders from the Avon Longitudinal Study of Parents and Children (ALSPAC). In ALSPAC, exposures included body mass index (BMI), waist hip ratio (WHR) and body fat percentage (BF); metabolomics data was available for up to 234 metabolites, which included metabolite ratios; data on available confounders included: age, sex, mothers or own education, smoking history, alcohol history, diet, physical activity. All analysis and data manipulation was performed using `R` (version 3.6.2)[146]. Specific `R` packages are described where appropriate. All code for this work is available on GitHub.

4.2.1 Overview: ALSPAC

ALSPAC[141,142,150] is a large prospective cohort study that invited women resident in Avon, UK with expected dates of delivery between 1st April 1991 and 31st December 1992 to participate. The initial number of pregnancies enrolled was 14,541 (for these at least one questionnaire has been returned or a "Children in Focus" clinic has been attended by 19/07/99). Of these initial pregnancies, a total of 14,676 fetuses, resulted in 14,062 live births and 13,988 children alive at one year of age.

When the oldest children were approximately seven years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrollment) that are currently represented on the built files and reflecting enrollment status at the age of 24 is 913 (456, 262 and 195 recruited during Phases II, III and IV respectively), resulting in an additional 913 children being enrolled. The phases of enrollment are described in more detail in the cohort profile paper and its update[141,142,150]. The total sample size for analyses using any data collected after the age of seven is therefore 15,454 pregnancies, resulting in 15,589 fetuses, of which 14,901 were alive at one year of age.

The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaire and clinics was obtained from participants following recommendations of the ALSPAC Ethics and Law Committee at the time. Full details of the ALSPAC consent procedures are available on the study website.

ALSPAC data is split by clinic visits. For this work, data for children was taken from the following clinics: Focus at 7 (~7 years old), Focus at 8 (~8 years old), Before Breakfast Study (~8 years old), Teen Focus 3 (~15 years old) Teen Focus 4 (~17 years old), Focus at 24 (~24 years old). Data on adults was taken from: Focus on Mothers 1 (~50 years old), Focus on Mothers 2 (~50 years old), and Focus on Fathers 1 (~50 years old). The Before Breakfast Study only collected metabolomics data, as such data on exposures and confounders were extracted for these individuals from the Focus at 8 clinic. Metabolomics data for each time point were extracted first and subsequent data on exposures and confounders were extracted for individuals with metabolomics data.

4.2.2 Outcomes: metabolites

There were slight differences in the methodology used across time points for the children and for the fathers metabolomics measurements. However, data are directly comparable (See the metabolomics data release file D5700 from the ALSPAC Data Dictionary). Briefly, high-throughput proton (^{1}H) nuclear magnetic resonance (NMR) assays were performed on EDTA plasma/serum samples. Samples were predominantly fasted. Measurements were taken at three molecular windows (lipoprotein lipids, low molecular-weight metabolites, and lipid extracts) enabling broad quantification of over 220 metabolomic measures. Full details on the NMR methodology has previously been described[151–154] and is available from the ALSPAC data dictionary (data dictionary identifiers: children = D5704, mothers = D5705, fathers = D5700). The Before Breakfast study does not have a documentation file and is described elsewhere[155]. Descriptions of metabolites are available in the Appendix A.4.1.

The spectral NMR data was processed by Nightingale Health and provided as a processed file with identifiable individuals (triplets/quadruplets) and individuals who had withdrawn consent removed. Some mothers and fathers were duplicated in the raw data due to the way in which mothers were originally enrolled into the study and assigned IDs. If a mother enrolled with two different pregnancies (both having an expected delivery date within the recruitment period (April 1991-December 1992)), she will have two separate IDs. A father associated with both of these pregnancies will also be duplicated. Duplicate measurements for mothers and fathers were removed. Raw metabolomics data was therefore available for: Focus at 7 (n = 5518; metabolites = 230), Before Breakfast Study (n = 640; metabolites = 228), Teen Focus 3 (n = 3371; metabolites = 230), Teen Focus 4 (n = 3175; metabolites = 230), Focus at 24 (n = 3269; metabolites = 224), Focus on Mothers 1 (n = 4362; metabolites = 230), Focus on Mothers 2 (n = 2708; metabolites = 230), Focus on Fathers (n = 1833; metabolites = 230).

In order to maximize the sample size at each clinic, data were combined where clinics were within a similar age range. For these combined data sets, duplicate individuals (i.e. those attending both clinics) were identified, and the measurement from the most recent clinic was dropped. The number of metabolites measured at each clinic visit for the children and adult data differed; unique metabolites were included in the combined data set. Raw, combined, metabolomics data was therefore available for: children (mean age (SD) = 7.56 (0.36); n = 5656; metabolites = 234), adolescents (mean age (SD) = 16.06 (1.11); n = 4489; metabolites = 230), young adults (mean age (SD) = 24.03 (0.85); n = 3269; metabolites = 224), adults (mean age (SD) = 49.53 (5.32)n = 6406; metabolites = 232; Table 4.1).

Quality control of the combined metabolite data (i.e. children, adolescents, young adults, adults) was performed using the `R` package `MetaboQC` (version 0.0.1). Quality control was performed twice, firstly including and secondly excluding the derived metabolomics measures from missingness and clustering. Briefly, individuals, and then metabolites, with high missingness (>=80%) were removed. Missingness was then re-calculated for individuals and metabolites, with removal based on 20% missingness. Individuals were then removed based on total sum abundance, considering outliers as > 5 standard deviations away from the mean. Using this metabolite data set, a dendrogram based on a Spearman's rho distance matrix is produced, and a set of clusters identified based on a Spearman's rho of 0.5. For each cluster, the metabolite with the least missingness is tagged as the representative feature. Finally, principal component analysis is conducted using the representative features to evaluate structure among individuals. Outliers are identified as being > 5 standard deviations away from the mean of principal component 1 and 2 and were excluded.

4.2.3 Exposures: measures of adiposity

Measures of adiposity (BMI, WHR, BF) were obtained for all individuals with available raw metabolomics data; identifiable individuals and those with withdrawn consent were therefore already excluded. As metabolomics measures were obtained on unique individuals where multiple clinics were attended, anthropometric data for these individuals were taken from the clinic associated with the metabolomic measure. No anthropometric data was available for the Before Breakfast Study, so the Focus at 8 clinic, as the most age appropriate clinic, was used instead. For this combined data, Focus at 7 measures were matched with Focus at 7 metabolomics measures and Focus at 8 measures were matched with Before Breakfast Study metabolomics measures.

Measures for children were taken from Focus at 7 and 8, for adolescents Teen Focus 3 and 4, for mothers Focus on Mothers 1 and 2, for fathers Focus on Fathers. Data on WHR was not available in adolescents. BMI was calculated as $\frac{weight(kg)}{height(m^2)}$ and WHR as $\frac{waist\ circumference\ (cm)}{hip\ circumference\ (cm)}$. BF was measured in adolescents, young adults, and adults using dual energy x-ray absorptiometry (DXA). Briefly, measurement required individuals to be prone and stationary while a Lunar prodigy narrow fan beam densitometer performed a whole body DXA scan. Data was processed using Lunar Prodigy software. Individuals did not have measurements taken if they: were pregnant; had a radiological investigation using contrast media within the week before the DXA scan; had a recent nuclear medicine investigation with persistent radioactivity; weighed greater than 159kg. BF was calculated as a percentage as $\frac{fat\ mass}{fat\ mass + fat\ free\ mass} * 100$. Available anthropometric measures for individuals with metabolomics data is given in Table 4.3 and distributions given in Figure 4.1.

In children, BF was not measured. A bioeletrical impedance measure was available; briefly, children were encouraged to pass urine and undress to their underclothes. A Tanita Body Fat Analyser (Model TBF 305) was used to measure weight and impedance. Height was entered to the nearest cm and 'female standard' was used for all children for sex. The Tanita Body Fat Analyser TBF 305 is a single frequency ($50kHz$) leg-to-leg device. In single frequency devices, impedance is a representation of resistance which is related to the volume of water (which one assumes makes up the majority of fat free mass (FFM)), as such, the higher the resistance/impedance the greater the amount of FFM. Calculation of BF from the impedance measure is only possible at the time of measurement, however these derived BF measures were not stored and the equation to calculate them was not available from the manufacturer (Appendix A.4.4).

Previous work[27] has shown that comparison of BF derived from the manufacturer's equation and an alternative[26] showed little difference in resulting BF. The equation was derived in a study involving 205 (101 women) healthy adults with a mean age of 43.8 (SD = 16) for men and 40.4 (SD = 13.6) for women. The equation, where Z is the impedance measure from the device in $ohms$, height is in meters, weight is in kilograms, age is in years, and female-specific components are given in parenthesis, is given as:

$$\begin{aligned} BF = -156.1 - 89.1\, ln(height) \\ + 45.6\, ln(weight) \\ + 0.120\, age \\ + 0.0494\, Z \\ + (19.6\, ln(height)) \end{aligned} \tag{4.1}$$

Given that the equation was derived from adult data, its application to child data was explored. A raw impedance measure, from a similar model (Tanita Body Fat Analyser (Model TBF 401A)), was obtained for adolescents and the equation was used to compare BF derived from the impedance device and BF measured with DXA in adolescents. Exploration involved visual inspection of distribution and Spearman's correlation with BMI, height, weight and other BF measures in adolescents. The same observations were carried out for raw impedance.

4.2.4 Confounders

Data on confounders were obtained for all individuals with raw metabolomics data; identifiable individuals and those with withdrawn consent were therefore already excluded. The following confounders were used: age, sex, maternal/own education, smoking, alcohol, diet, physical activity. Age was taken from the metabolomics clinic visit. The number of individuals with available data is given in Table 4.4.

Maternal education was used for children, adolescents and young adults. Own education was used for mothers and mother reported partner education was used for fathers. Specifically, mothers were asked, during their pregnancy, ‘What educational qualifications do you, your partner, your mother, and your father have?’ with possible answers: CSE or GCSE (D, E, F or G), O-level or GCSE (A, B, or C), A-level, qualifications in shorthand/ typing/or other skills, e.g. hairdressing, apprenticeship, state enrolled nurse, state registered nurse, City and Guilds intermediate technical, City & Guilds final technical, City & Guilds full technical, teaching qualification, university degree, no qualification, qualifications not known, not applicable, other (please describe).

Smoking was binary; adolescents (at the metabolomics clinic), young adults (at the metabolomics clinic), and adults (mothers were asked during pregnancy; fathers were asked in 2013) were asked whether they had ever smoked a cigarette before.

Adolescents (Teen Focus 3) were asked what their alcohol drinking pattern was with possible answers: only ever tried drinking once/twice, used to drink sometimes [but] never drink now, sometimes drink but less than once a week, usually drink on 1/2 days a week, usually drink on >2 days a week but not every day, usually drink every day. Adolescents (Teen Focus 4), young adults (at the metabolomics clinic), mothers (in 2013), and fathers (at the metabolomics clinic) were asked the frequency they had drinks containing alcohol with possible answers: never, monthly or less, two to four times a month, two to three times a week, four or more times a week.

Diet data, as predicted kilo-calories consumed per day, was derived from Anderson et al. (2013)[156] and avaialble for ages 7 and 13. Data from age 7 was matched with metabolomics data for children while data from age 13 was matched with adolescents. Diet data was not available for young adults or adults.

In adolescents and young adults, accelerometry data was collected at the same clinic for which metabolomics data were collected. Briefly, individuals wore an accelerometry device for the days following their clinic visit whilst keeping a diary of the times they wore and took off the device. Individuals were advised to wear the accelerometer device if the following days were part of a 'normal week' with regards to their activity. For young adults, physical activity data is the average number of minutes per day spent doing moderate to vigorous physical activity. For adolescents, data was available from Teen Focus 3 and is the mean counts per minute spent doing moderate to vigorous physical activity for the whole week. Adults were asked 'do you take part in physical activity (e.g. running, swimming, dancing, golf, tennis, squash, jogging, bowls)?' with possible answers: no, occasionally (less than monthly), frequently (once a month or more). Data for mothers was available in 2010, fathers data was available at the metabolomics clinic. Physical activity data was not available for children.

4.2.5 Statistical analysis

To investigate the association between measures of adiposity and metabolites, all exposures were Z-scored and linear regression was performed. Variables known to influence the metabolomic profile and adiposity (age[157,158], sex[158], education[159], smoking[160], alcohol[160], diet[161], and physical activity[162]), were included as confounders. Three linear models were used to investigate potential effects of these confounding variables. Model 1 included age at the metabolomics clinic visit and sex. Model 2 included model 1 and mothers/own level of highest education, whether respondent had ever smoked, frequency respondent had a drink containing alcohol, and predicted kilo-calories consumed per day (diet). Model 3 comprised model 2 and physical activity. For models 1 and 2, individuals with data on all confounders except physical activity were included. Model 3 comprised all individuals included in model 1 and 2 who also had data on physical activity.

For all analyses, the units represent the absolute change in each metabolite per standard deviation change in the exposure. Ninety-five percent confidence intervals were calculated and a multiple testing threshold specific for each group was applied. Multiple testing thresholds were calculated as the number of independent metabolites within the raw data given a Spearman's rho of approximately 0.75 among the metabolites with data for at least 20% of samples – this was calculated during metabolite quality control. The number of independent metabolites in each group was: children = 42, adolescents = 42, young adults = 40, adults = 44.

Presentation

Metabolites were grouped into subclasses (grouping data provided by the metabolomics platform) based on biological pathway. Model 2, as the most adjusted and given the reduced sample size in Model 3, is presented as the main analysis for this work. Consistency in the direction of effect estimates across models within each exposure and age group was investigated, as was the number of tests reaching a multiple testing threshold. Directional consistency was investigated for exposures across age groups for model 2. A Spearmans Rho analysis was used to investigate the correlation between effect estimates across exposures and age groups. Visualization and comparison of global metabolic profiles across exposures within age groups, and within exposures and across age groups was performed using Circos plots using the `EpiViz` `R` package[]. Forestplots, created using the `ggforestplot` `R` package, were used to examine specific subclasses where variation among metabolites within the subclass and strong effects were identified. Results for derived measures and *Lipoprotein particle size* and *Fatty acid ratios* are presented in the supplement. Effect estimates were compared to that of previous work by Wurtz et al. (2014)[149].

4.3 Results

In total, metabolomics data was available for 234 metabolites in children (N = 5656), 230 metabolites in adolescents (N = 4489), 224 metabolites in young adults (N = 3269), and 232 metabolites in adults (N = 6406; Table 4.1). Quality control was performed twice, firstly including derived metabolites and secondly excluding them. There was a large difference in the number of representative features identified across the two runs, as such quality controlled data used here on was produced having included derived metabolites.

Quality control resulted in: 6 individuals and 4 metabolites removed from the children's data (4 samples excluded for >= 80% missingness; 1 sample excluded for total sum abundance >= 5 SD from the mean; 1 sample excluded as a result of being >= 5 SD from the mean of PC1 and 2; 4 metabolites removed for >= 20% missingness), 5 individuals and 0 metabolites removed from the adolescents data (1 sample excluded for total sum abundance >= 5 SD from the mean; 4 samples excluded as a result of being >= 5 SD from the mean of PC1 and 2), 4 individuals and 0 metabolites removed from the young adults data (1 sample excluded for total sum abundance >= 5 SD from the mean; 3 sample excluded as a result of being >= 5 SD from the mean of PC1 and 2), 7 individuals and 4 metabolites removed from the adults data (1 sample excluded for total sum abundance >= 5 SD from the mean; 6 samples excluded as a eresult of being >= 5 SD from the mean of PC1 and 2; 4 metabolites removed for >= 20% missingness). Quality controlled metabolomics data available for analysis is given in Table 4.2. A total of 220 metabolites were measured in all age groups. Of individuals with metabolomics data, a majority also had data on measures of adiposity (Table 4.3 and Figure 4.1), except for adolescents where data on WHR was not available. Data on confounders were also available in the majority of individuals, the exception being phsyical activity where much fewer individuals had available data and no data was available for children (Table 4.3.

Table 4.1: Metabolomics data available in ALSPAC

Combined group	N	N metabolites	Subgroup	Subgroup N	Unique N	Total metabolites	Unique metabolites
Children	5656	234	7	5518	5016	230	5
			8	640	138	228	7
Adolescents	4489	230	15	3371	1314	230	0
			17	3175	1118	230	0
Young adults	3269	224	24	3269	–	224	–
Mothers	4573	230	Focus on mothers 1	4362	1865	230	0
			Focus on mothers 2	2708	211	230	0
Fathers	1833		Focus on fathers	1833	–	230	–
Adults	6406	232	Mothers	4573	–	230	2
			Fathers	1833	–	230	2

Table 4.1: the number of individuals with metabolomics data in ALSPAC. Children were measured at 5 time points and combined into three groups (Children, Adolescents, Young adults). Mothers were measured at two time points and combined. Fathers were measured at a single time point. Combined mothers and the fathers data were grouped as Adults. N = number of individuals in the Combined group; N metabolites = the number of metabolites measured in the Combined group; Subgroup = age or clinic identifier; Subgroup N = number of individuals in the Subgroup; Unique N = the number of individuals in the subgroup who do not appear in the other subgroup;

Total metabolites = the number of metabolites measured for the Subgroup; Unique metabolites = as with Unique N, the total number of metabolites measured in the Subgroup not measured in the other Subgroup of that Combined group.

Table 4.2: Quality controlled metabolomics data available in ALSPAC

Group	N	Metabolites
Children	5650	230
Adolescents	4484	230
Young_adults	3265	224
Adults	6399	228

Table 4.2: the number of individuals and metabolites available in ALSPAC after quality control of metabolomics data. Group = the groups clinic visits were combined into; N = number of individuals with available metabolomics data after quality control; Metabolites = the number of metabolites measured in the Group after quality control.

Table 4.3: measures of adiposity available for individuals with metabolomics data

Group	N	BMI N	mean	SD	WHR N	mean	SD	BF N	mean	SD
Children	5650	5622	16.20	2.00	5589	0.86	0.04	5381	-	-
Adolescents	4484	4404	21.71	3.68	-	-	-	4210	25.65	11.7
Young_adults	3265	3230	24.73	4.88	3223	0.8	0.07	3153	31.75	9.22
Adults	6399	6352	26.83	4.98	6360	0.85	0.09	6138	34	9.08

Table 4.3 gives information on measures of adiposity for individuals with metabolomics data. Measures were obtained for all individuals who had raw metabolomics data; WHR was not available for adolescents. Group = the groups clinic visits were combined into; Data = whether the data presented is for the raw or the QC'd metabolomics data; N = the number of individuals with available data; mean = the mean of the anthropometric measure; SD = standard deviation of the mean. NA = data not available.

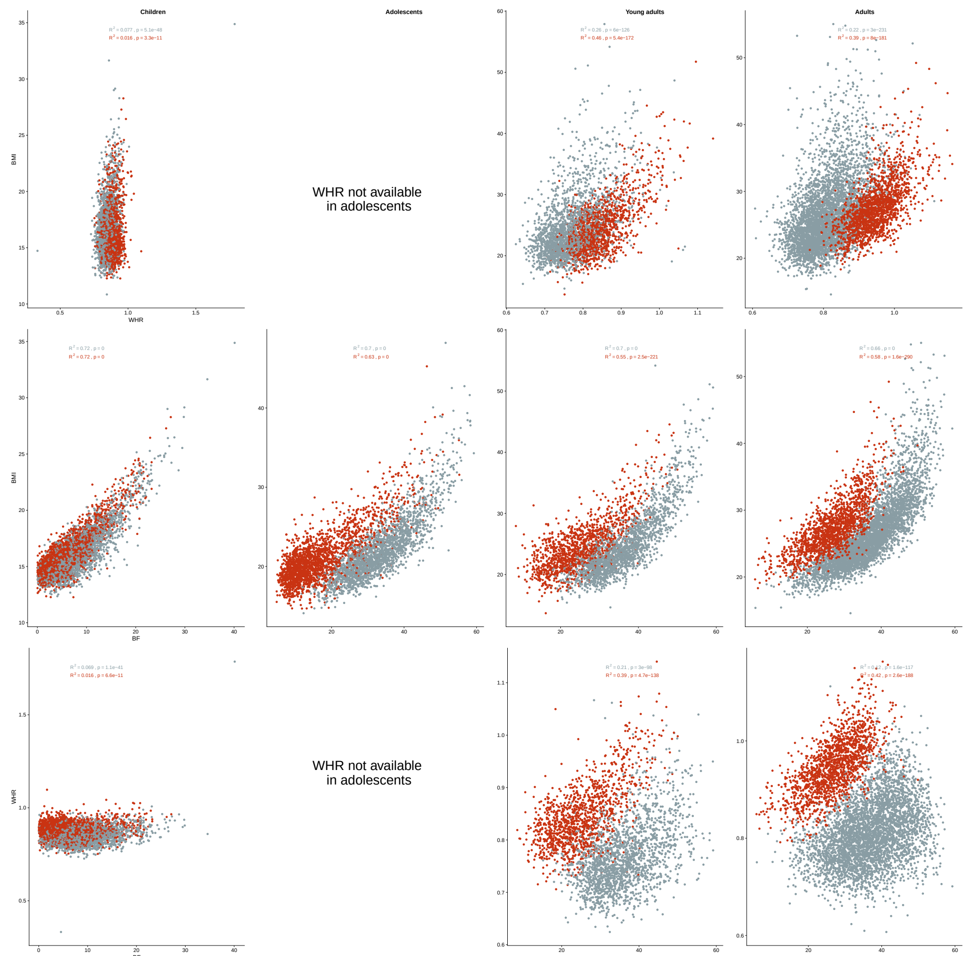

Figure 4.1: Raincloud plots of ALSPAC individuals data on measures of adiposity

Figure 4.1 shows the distribution of adiposity measures among different groups separated by sex. Data is presented for individuals with pre-QC metabolomics data and of known sex. The interquartile range and median are also shown. From left to right: children, adolescents, young adults, adults. From top to bottom: body mass index (BMI), waist hip ratio (WHR), body fat percentage (BF). Red = male; grey = female. Raincloud plots produced using the `RainCloudPlots` *R package*[163]

Table 4.4: Confounders available for individuals with raw metabolomics data

		Children	Adolescents	Young adults	Adults
Metabolomics	N	5650	4484.00	3265	6399
Age	N	5634	4474.00	3264	6381
	Mean	7.56	16.06	24.03	49.53
	SD	0.36	1.11	0.85	5.32
Sex	N	5634	4474.00	3265	6390
	Female	2727	2340.00	1966	4557
Education	1	8.55	7.67	6.16	6.44
	2	7.68	6.87	6.19	6.13
	3	31.82	30.55	29.95	27.89
	4	24.23	26.05	26.22	26.83
	5	15.33	16.61	18.74	21.35
Smoking	N	-	2499.00	3219	5854
Alcohol	1	-	8.79	2.7	5.69
	2	-	7.49	20.46	9.17
	3	-	45.43	37.46	16.28
	4	-	16.93	30.57	27.05
	5	-	3.41	5.27	18.89
	N	5577	4338.00	-	-
	Mean	1672.32	2252.32	-	-

Diet	SD	134.94	190.62	-	-
Physical activity	N/1	-	1768.00	672	24.43
	Mean/2	-	483.67	50.23	10.3
	SD/3	-	179.39	30.24	36.41

Table 4.4 gives information on confounders for individuals with metabolomics data. Data on confounders were obtained for all individuals who had raw metabolomics data. Smoking and alcohol data were not available for children. Diet was not available for young adults and adults. Physical activity data was not available for children. Education is highest level of education; for children, adolescents, and young adults education is maternal education; for adults education is own education. Smoking is binary. Alcohol is frequency respondent consumes an alcoholic drink, with 1 being low and 5 high. Diet is predicted kilo-calories consumed per day derived from Anderson et al. (2013)[156]. Physical activity in adolescents is mean counts per minute of activity across 7 days (based on valid days). For young adults physical activity is the average number of valid minutes per day spent doing moderate to vigorous activity. For adults, physical activity is: no physical activity (1), occasionally (2), frequently (3). Group = the groups clinic visits were combined into; N = the number of individuals with available data; mean = the mean of the measure; SD = standard deviation of the mean. - = data not available.

4.3.1 Validation of impedance

In children, a measure of BF was not available. Instead, impedance ($ohms$) was used to calculate (Equation (4.1)) BF. The calculated BF resulted in negative estimates of BF for some children (Figure 4.2). The calculated BF was positively correlated with weight, height and BMI in children. In adolescents, the calculated BF did not produce negative estimates and was positively correlated with impedance and DXA derived BF estimates (Figure 4.3), as well as with weight, height, and BMI (Figure 4.4). Child calculated BF positively correlated with adolescent measures of BF (Figure 4.3). Impedance in children and adolescents negatively correlated with BMI and weight, but showed little evidence for a correlation with height (Figure 4.2). Similarly, there was weak evidence for correlation between impedance in children and adolescents and adolescent measures of BF (Figure 4.3).

Equation (4.1) was derived using adult data; given the volumetric difference between adults and children (BMI cubed rather than BMI squared may be more appropriate in children[164]) differences in the range of estimates is unsurprising. As there is strong correlation between calculated BF and other measures of BF in adolescents, and with weight, height and BMI in children even with negative estimates, and that in a linear model the estimate is based on the per-unit increase, the absolute value of the exposure does not, in this instance, need to be positive. As such, BF calculated using equation (4.1) was used in subsequent analyses.

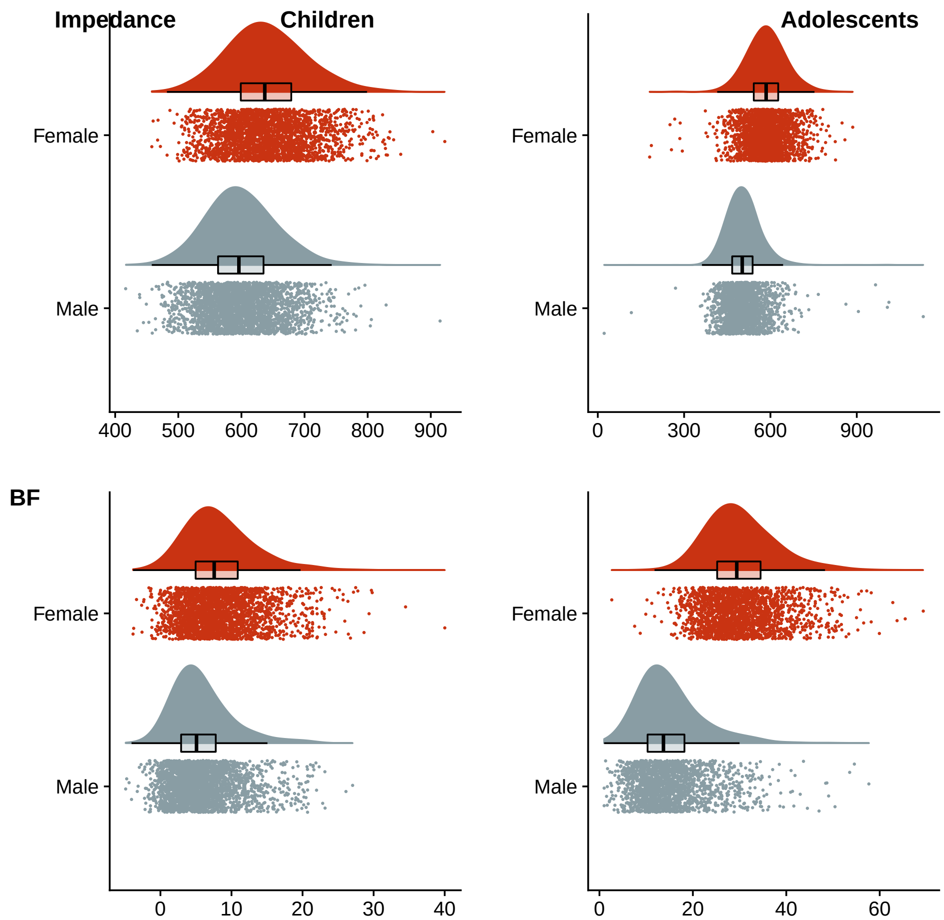

Figure 4.2: Raincloud plots of impedance and BF in children and adolescents

1307 *Figure 4.2 shows the distribution of the raw impedance value measured in* $ohms$ *and BF*
1308 *derived using equation* (4.1) *for children and adolescents. Data is presented for complete*
1309 *cases across: raw metabolomics, BMI, WHR (children only), impedance, height, weight,*
1310 *age, sex, and BF derived by impedance and DXA in adolescents. The interquartile range*
1311 *and median are also shown. Data is organised with males at the top and females at the*
1312 *bottom of each individual plot. Raincloud plots produced using the* `RainCloudPlots`

R *package*[163]

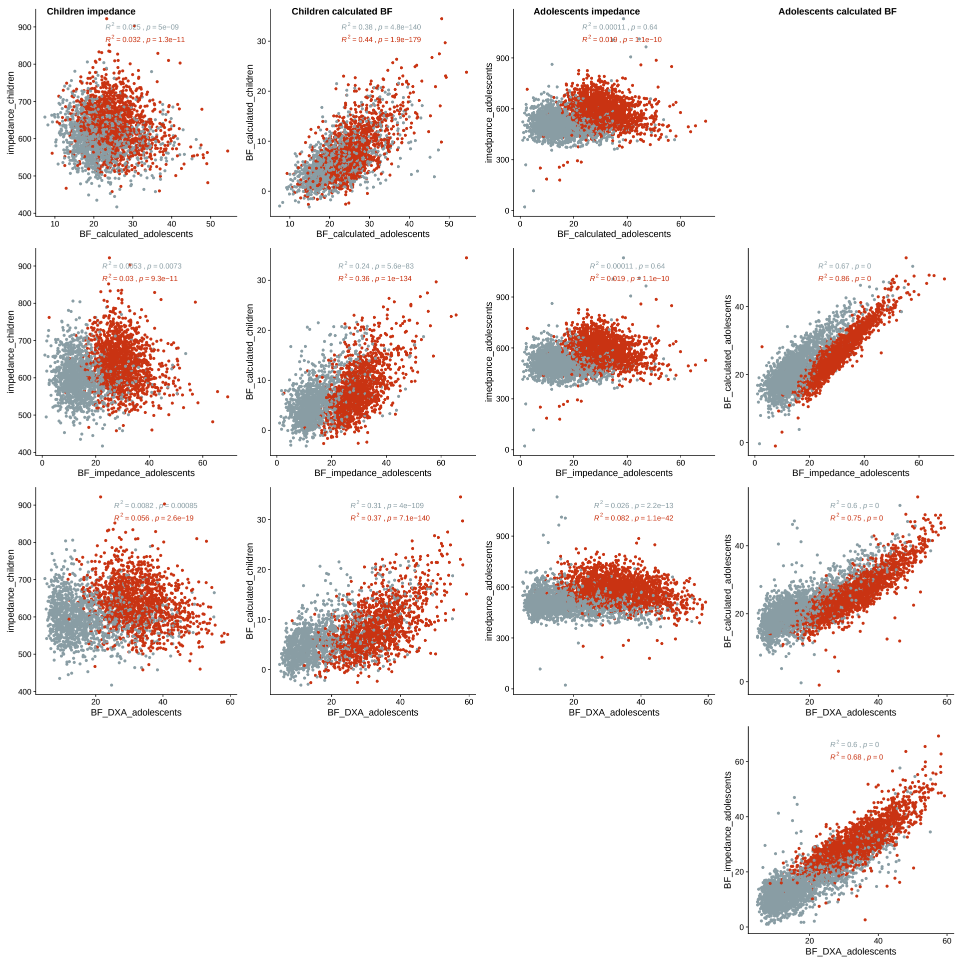

Figure 4.3: Correlation between differnet BF measures in children and adolescents

Figure 4.3 shows correlations for BF calculated using equation (4.1) *in children and adolescents. Column 1 shows correlations between child impedance values and adolescent BF estimates. Column 2 shows correlations for child calculated BF and adolescent BF estimates. Column 3 shows correlations for adolescent calculated BF and adolescent BF estimates. Data is presented for complete cases across: QC'd metabolomics, BMI, WHR* *(children only), impedance, height, weight, age, sex, and BF derived by impedance and DXA in adolescents. Data for men is shown in grey and women in red.*

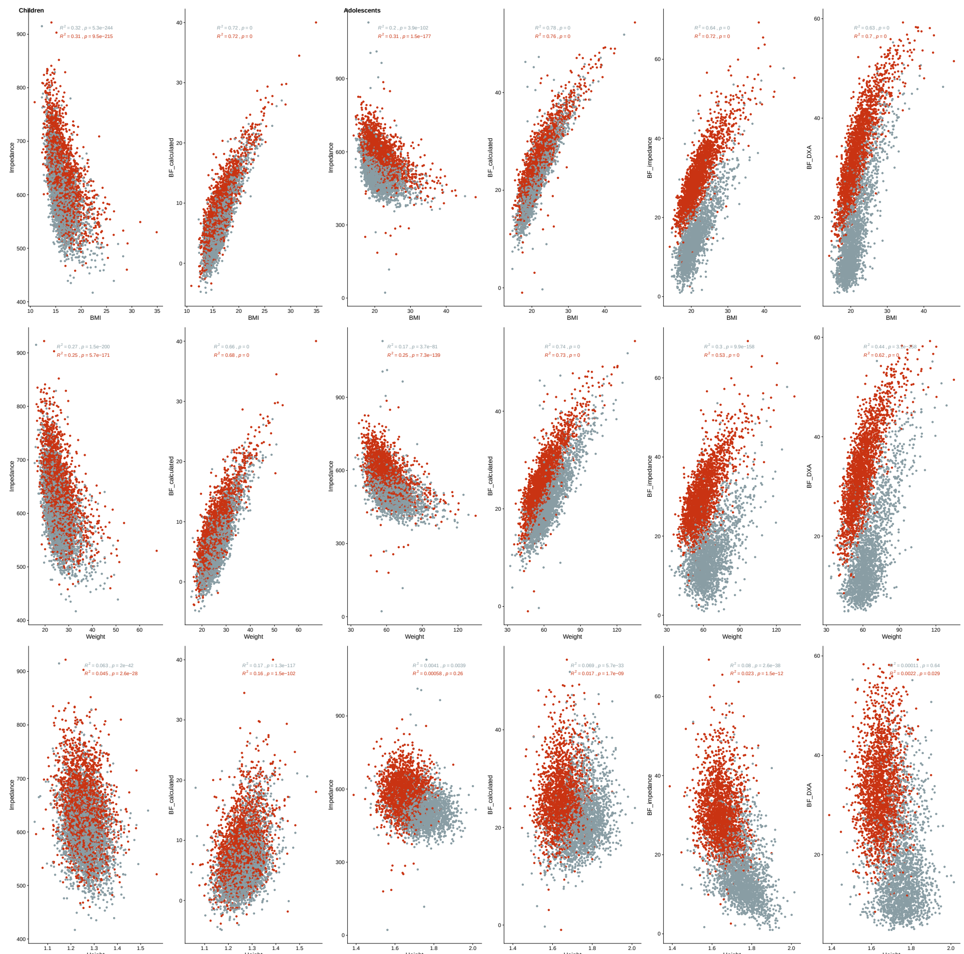

Figure 4.4: Correlation between BF and BMI, height, and weight in children and adolescents

Figure 4.4 shows correlations for impedance and BF for children (columns 1 and 2) and adolescents (columns 3-6) with BMI (top row), weight (middle row), and height (bottom row). BF_calculates is BF derived using the raw impedance value measured in ohms and *equation* (4.1)*. Data is presented for complete cases across: QC'd metabolomics, BMI, WHR (children only), impedance, height, weight, age, sex, and BF derived by impedance and DXA in adolescents. Data for men is shown in grey and women in red.*

4.3.2 Statistical analysis

Directional consistency: across models within exposures and age groups

Across models within each exposure and age group a majority of tests resulted in directionally consistent effect estimates (Figure 4.5). Of these directionally consistent effects, the majority of effect estimates were positive. The strength of the effect estimates were broadly consistent across models; confidence intervals overlapped across the majority of metabolites for all models within each group and exposure (Supplementary A.4.5). Of the 220 metabolites measured in all age groups, directional consistency was supported by strong evidence of correlation across models within exposures and age groups (Supplement A.4.3).

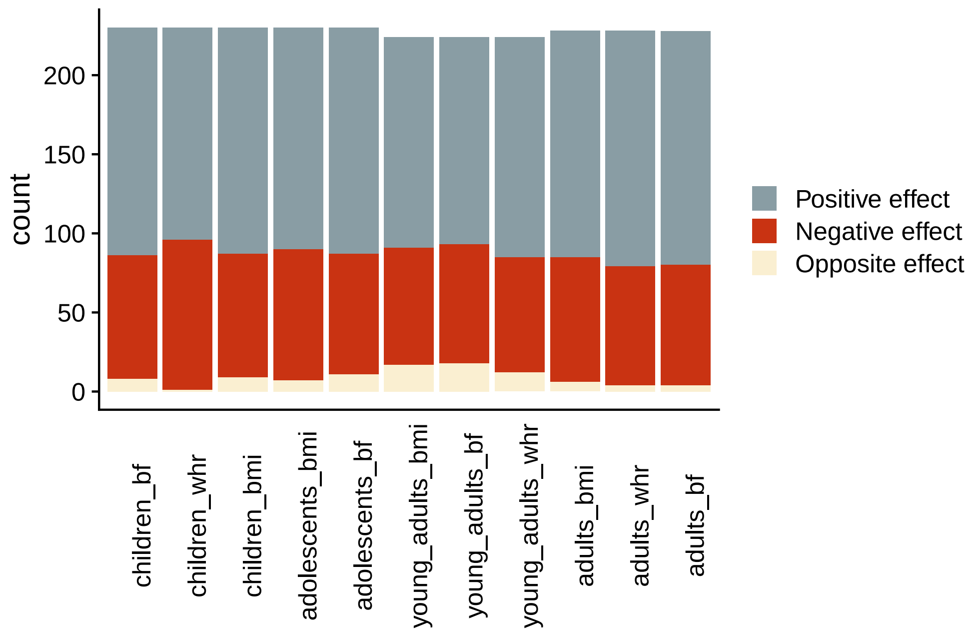

Figure 4.5: Directional consistency across linear models

Figure 4.5 shows the directional consistency of all models for each group and exposure A positive effect reflects both model betas being in the positive direction; a negative effect reflects both model betas being in a negative direction; opposite effect reflects different directions for the model betas. BMI = body mass index; WHR = waist hip ratio; FFM = fat free mass; BF = body fat percentage.

Multiple testing threshold

Across all models and exposures, between 32.61 percent and 86.4 percent (median = 61.3 percent) of metabolites reached a multiple testing threshold (children multiple testing threshold = 42, adolescents = 42, young adults = 40, adults = 44; Table 4.5). Of those with a consistent direction of effect across the three exposures a total of 109, 146, 164, and 180 metabolites reached a multiple testing threshold for children, adolescents, young adults, and adults respectively. This equates to 47, 63, 73, and 79 percent of metabolites.

Table 4.5: Metabolites reaching a multiple testing threshold

		BMI			WHR			BF		
	N	1	2	3	1	2	3	1	2	3
Children	230	141	137	–	148	148	–	141	132	–
Adolescents	230	138	156	83	–	–	–	150	159	75
Young adults	224	173	172	139	173	172	139	183	180	135
Adults	228	193	191	183	193	191	183	197	191	186

Table 4.5 shows the number of metabolites reaching a multiple testing threshold for each model within each age group. Multiple testing thresholds: children = 54, adolescents = 48, young adults = 46, adults = 53. N = total number of metabolites tested; BMI = body mass index; WHR = waist hip ratio; BF = body fat percentage (in children this is fat free mass); 1 = model 1 adjustment for age and sex; 2 = model 2 adjustment for model 1 plus maternal/own education, smoking status, alcohol frequency, diet (where available); 3 = model 3, adjustment for model 2 plus physical activity (where available).

Directional consistency: across exposures within age groups for model 2

Results here on are presented for model 2 only; results for models 1 and 3 are presented in the supplement. Across exposures within each age group, effects showed mostly consistent directions of effect, with the majority being positive

(Figure 4.6). The most inconsistent directions across exposures were found for children, where 21 percent of metabolites showed inconsistent directions of effect. For adolescents, young adults, and adults 5, 9, and 5 percent of metabolites showed inconsistent effect directions across measures of adiposity respectively. Of the 220 metabolites measured across all age groups, directional consistency was supported by strong evidence of correlation across exposures within age groups; though still strong, weaker correlations were observed when looking within exposures across age groups (Supplement A.4.3).

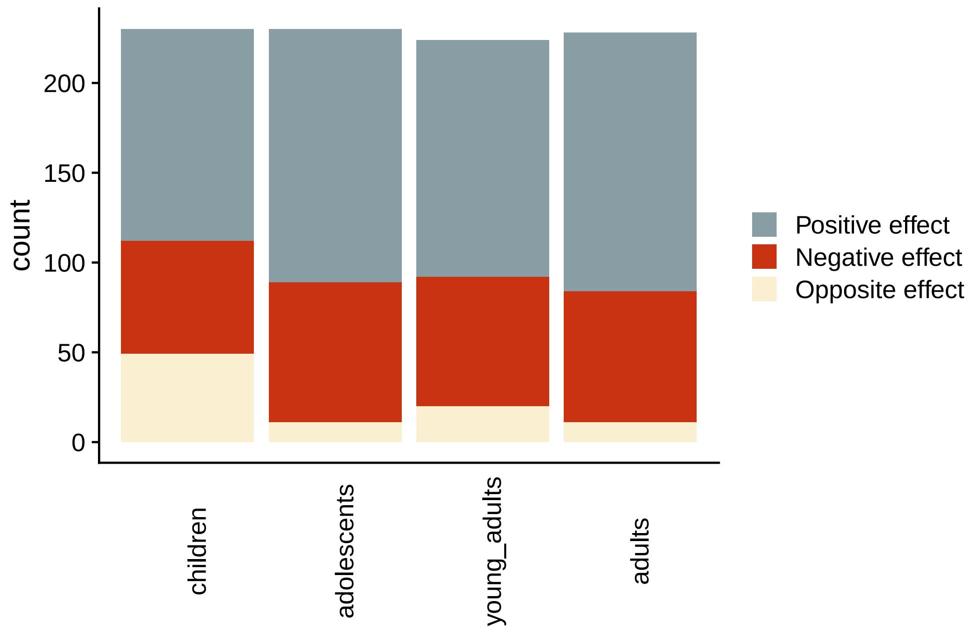

Figure 4.6: Directional consistency across exposures within each age group

Figure 4.6 shows the directional consistency of all exposures for each age group. A positive effect reflects effect estimates for all exposures being in the positive direction; a negative effect reflects effect estimates being in the negative direction; opposite effect reflects different directions for the effect estimates across the exposures.

Global metabolic profile

Globally, the pattern of association was very similar for all measures of adiposity for children (Figure 4.7), adolescents (Figure 4.8), young adults (Figure 4.9), and adults (Figure 4.10). Across all age groups the largest effects were found for the *Fatty Acids* subclass; total fatty acids showed the largest effect for all age groups. Metabolites in subclasses *small VLDL*, *medium VLDL*, *large VLDL*, and *very large VLDL* were the only ones to reach the specified significance thresholds across all exposures and age groups. Effect estimates for derived measures were much higher for all exposures and age groups than with the subclasses presented here (Supplementary A.4.5). There was also considerable variation within subclasses for derived measures. The largest effect across all age groups and exposures among derived measures was observed for *Cholesterol esters in very large VLDL to total lipids in very large VLDL ratio* and *Total cholesterol in very large VLDL to total lipids in very large VLDL ratio*. Across age groups, direction of effect was consistent for the majority of metabolites within exposures (Supplementary A.4.5). On the whole, effect sizes were lowest in children and increased with age. The largest effect in adults, *Total fatty acids* (beta = 0.51), was over twice that observed in children (beta = 0.21).

Figure 4.7: Circos plot of effect estimates from a linear regression of measures of increased adipsoity and metabolites in children

Figure 4.7 shows each track as one of the measures of adiposity; the outer track is BMI, the middle track is WHR, the inner track is BF. Solid points indicate a multiple testing threshold has been reached – threshold set to the lowest of the age groups (54).

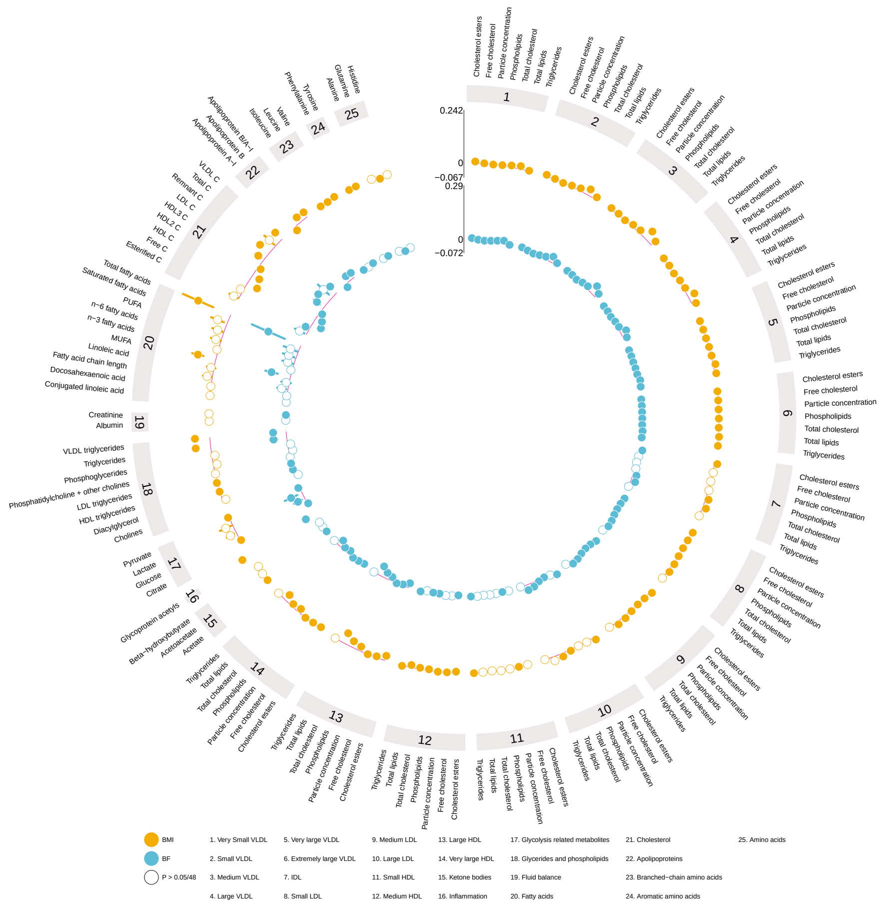

Figure 4.8: Circos plot of effect estimates from a linear regression of measures of increased adipsoity and metabolites in adolescents

Figure 4.8 shows each track as one of the measures of adiposity; the outer track is BMI, the other track is BF - WHR was not available for adolescents. Solid points indicate a multiple testing threshold has been reached – threshold set to the lowest of the age groups (48).

Figure 4.9: Circos plot of effect estimates from a linear regression of measures of increased adipsoity and metabolites in young adults

Figure 4.9 shows each track as one of the measures of adiposity; the outer track is BMI, the middle track is WHR, the inner track is BF. Solid points indicate a multiple testing threshold has been reached – threshold set to the lowest of the age groups (46).

Figure 4.10: Circos plot of effect estimates from a linear regression of measures of increased adipsoity and metabolites in adults

1401 *Figure 4.10 shows each track as one of the measures of adiposity; the outer track is BMI, the middle track is WHR, the inner track is BF. Solid points indicate a multiple testing threshold has been reached – threshold set to the lowest of the age groups (53).*

Subclass results

At the level of the subclass, associations were observed for all measures of adiposity across age groups and every subclass except *Large LDL* in children, where weak evidence of association was observed across measures of adiposity. Across the derived measures, associations were observed across measures of adiposity for all subclasses except *Extremely large VLDL ratios* in young adults and adults.

Across all age groups and exposures associations with every metabolite in a particular subclass was observed for *Small VLDL*, *Medium VLDL*, *Large VLDL*, *Very large VLDL*, and *Extremely large VLDL* (Figure 4.11). As age increased, the number of associations within subclasses tended to increase across all measures of adiposity. For example, across *Small LDL*, *Medium LDL*, and *Large LDL* few associations were observed across measures of adiposity in children, however in adolescents and young adults a majority of metabolites showed evidence of association while in adults all metabolites showed evidence of association.

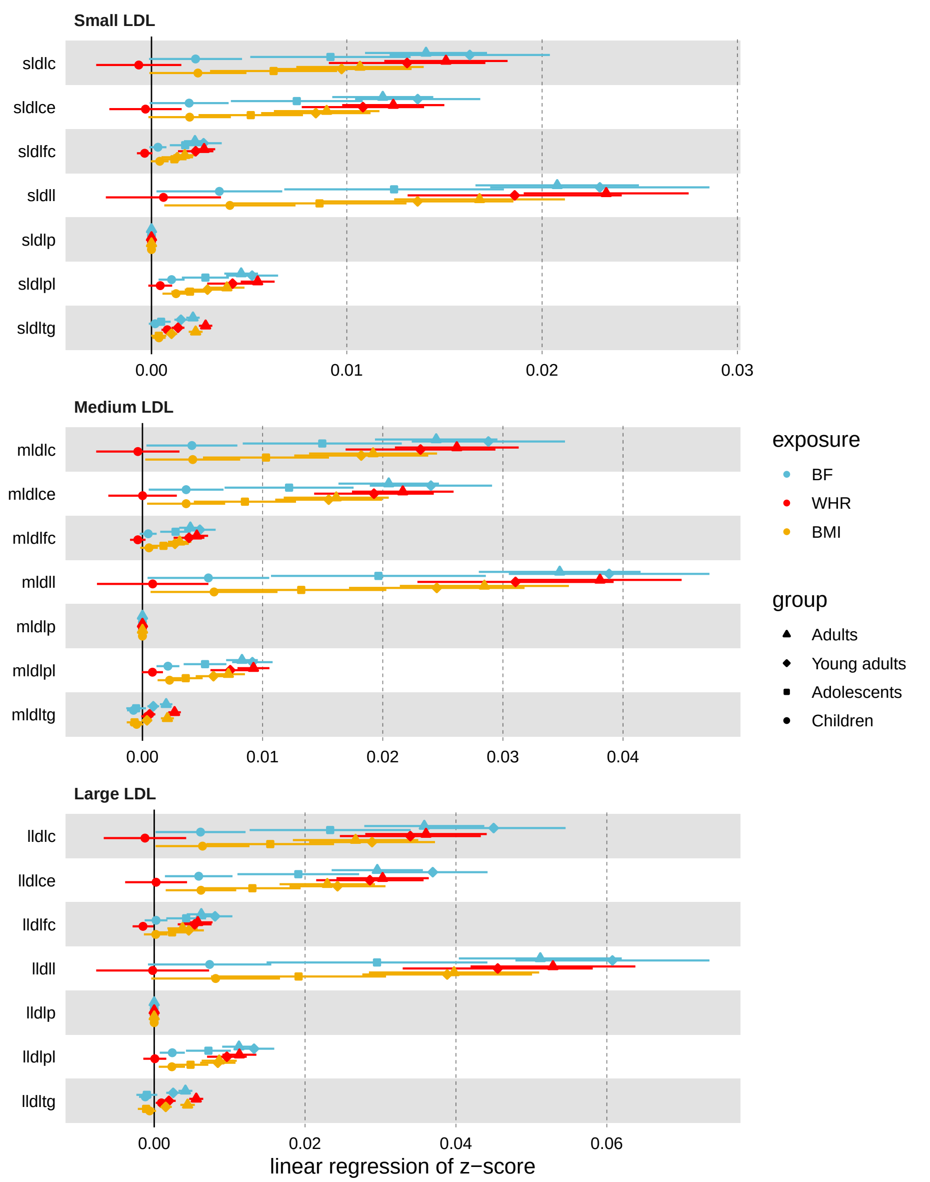

Figure 4.11: Forestplot of effect estimates across exposures and ages for LDL subclasses

Figure 4.11 gives the effect estimate and 95% confidence interval for model 2 across all *exposures and age groups.*

Individual results

Excluding derived measures, *Fatty acids ratios*, and *Lipoprotein particle size* subclasses, which showed much larger and varied effects compared to other subclasses, effects ranged from -0.12 to 1 with a median of 0.003. The largest positive effects (> 0.1) were seen for Total fatty acids and mono-unsaturated fatty acids; the largest negative effects (< -0.1) were for Total lipids in large HDL and Total cholesterol in HDL (Table 4.6).

Table 4.6: Largest effects (<= -0.1 and => 0.1) found across exposures and age groups

Metabolite	Subclass	Group	Exposure	Beta	Lower CI	Upper CI
Remnant cholesterol (non-HDL, non-LDL -cholesterol) (mmol/l)	Cholesterol	young_adults	bf	0.11	0.10	0.13
		adults	whr	0.10	0.09	0.12
Serum total cholesterol (mmol/l)		young_adults	bf	0.11	0.08	0.15
Monounsaturated fatty acids; 16:1, 18:1 (mmol/l)		adults	whr	0.22	0.20	0.25
			bmi	0.21	0.18	0.23
			bf	0.20	0.18	0.23
		young_adults		0.20	0.17	0.23
			whr	0.17	0.14	0.20
			bmi	0.14	0.11	0.17
		adolescents	bf	0.10	0.07	0.14
		adults	whr	0.20	0.17	0.22

	young_adults	bf	0.16	0.13	0.19
	adults	bmi	0.16	0.13	0.18
	adults	bf	0.15	0.13	0.18
Saturated fatty acids (mmol/l)	young_adults	whr	0.14	0.11	0.17
	young_adults	bmi	0.11	0.08	0.14
	adults	whr	0.50	0.44	0.57
	young_adults	bf	0.45	0.36	0.54
	adults	bf	0.43	0.36	0.49
	adults	bmi	0.41	0.34	0.48
	young_adults	whr	0.39	0.30	0.48
	young_adults	bmi	0.30	0.22	0.38
	children	whr	0.21	0.16	0.26
	adolescents	bf	0.19	0.09	0.29
	children		0.18	0.12	0.24

Total fatty acids (mmol/l)		adolescents	bmi	0.16	0.09	0.24
		children	bf	0.12	0.07	0.18
Serum total triglycerides (mmol/l)		adults	whr	0.18	0.17	0.20
			bmi	0.16	0.15	0.18
		young_adults	bf	0.16	0.14	0.17
			whr	0.15	0.14	0.17
		adults	bf	0.14	0.13	0.16
		young_adults	bmi	0.13	0.12	0.15
Triglycerides in VLDL (mmol/l)	Glycerides and phospholipids	adults	whr	0.16	0.15	0.17
		young_adults	bf	0.14	0.13	0.16
		adults	bmi	0.14	0.13	0.16
		young_adults	whr	0.14	0.13	0.15
		adults	bf	0.13	0.11	0.14
		young_adults		0.12	0.11	0.13

Glucose (mmol/l)	Glycolysis related metabolites	adults	bmi	0.17	0.14	0.20
			whr	0.16	0.13	0.19
			bf	0.11	0.08	0.14
Total lipids in large HDL (mmol/l)	Large HDL	young_adults	bf	-0.10	-0.11	-0.09
		adults	bf	-0.10	-0.11	-0.09
		young_adults	whr	-0.11	-0.12	-0.09
		adults	bmi	-0.12	-0.13	-0.11
		adults	whr	-0.12	-0.13	-0.11
Total lipids in medium VLDL (mmol/l)	Medium VLDL	adults	whr	0.10	0.09	0.11

Results only shown for model 2. All results reported a P-value < 1.17×10^{-4}.

Comparison with Wurtz et al. (2014)[149]

A total of 84 metabolic measures, including systolic and diastolic blood pressure, where measured by Wurtz et al. (2014)[149]. Of these, 42 were comparable with metabolites measured here. Direction of effect estimates were broadly similar across both studies (Figure 4.12). The size of the effects among *IDL*, *Lipoprotein particle size*, *Glycolysis related metabolites*, *Fatty acids ratios*, *Fatty acids*, *Cholesterol*, and *Apolipoproteins* were, bar a few metabolites within the subclasses, broadly similar; large confidence intervals among analysis conducted here among *Glycolysis related metabolites* meant effects overlapped with those of Wurtz et al (2014). Effects on metabolites in the remaining subclasses were much larger in the Wurtz et al. (2014) analysis than that conducted here; this is particularly evident for *Amino acids*, *Aromatic amino acids*, and *Branched-chain amino acids*. .

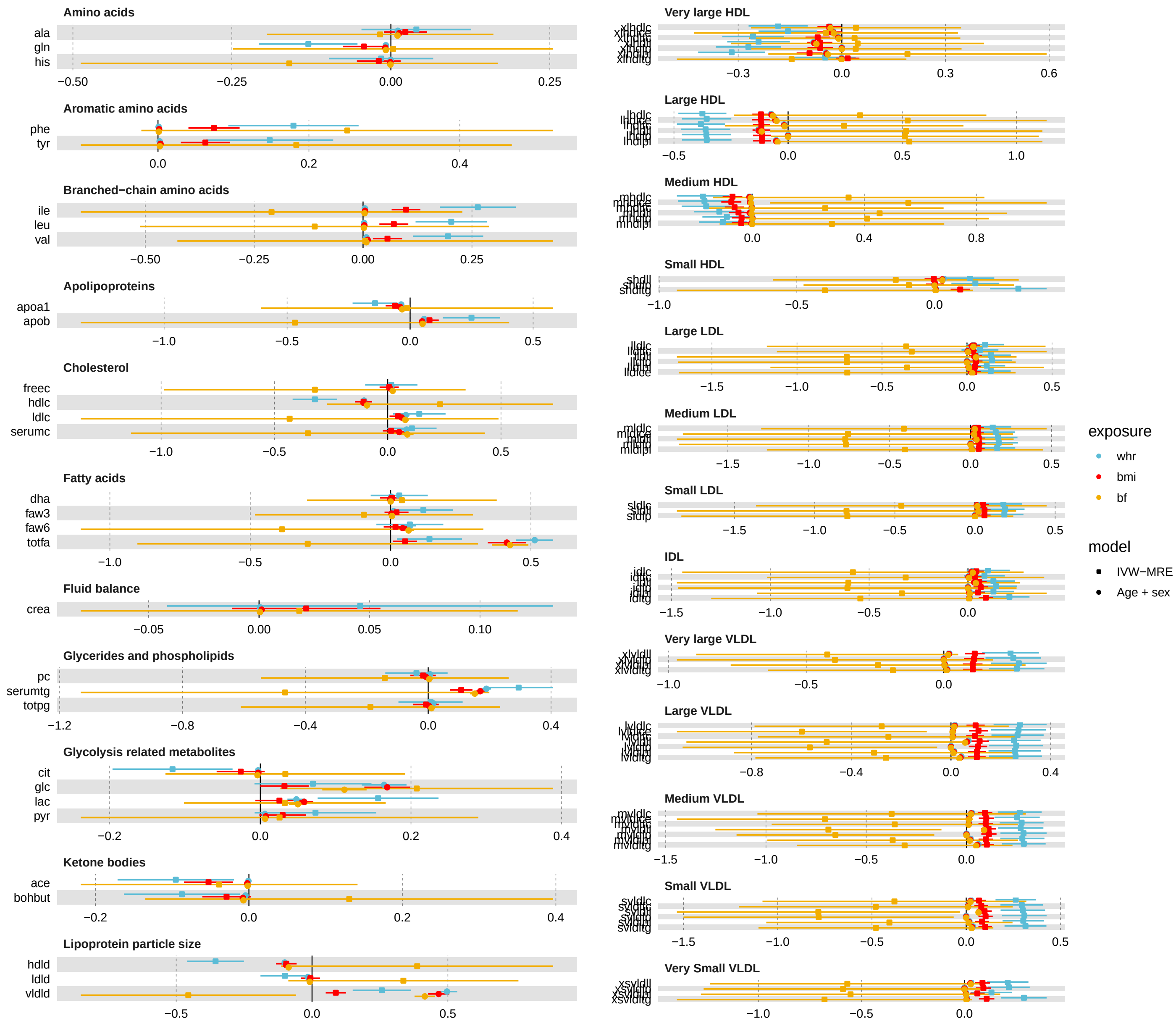

Figure 4.12: Forestplot of effect estimates across exposures and ages for LDL subclasses

Figure 4.12 gives the effect estimate and 95% confidence interval for model 2 across all exposures and age groups.

4.4 Discussion

In this chapter, the influence of increased adiposity on the metabolic profile is demonstrated in an observational framework. These effects persist, not only when measured at different ages, but also when adjusted for confounders and when examined across multiple measures of adiposity.

The association between increased adiposity and metabolites is global, with effects seen across all subclasses of metabolites. These effects are broadly consistent between metabolites within each subclass. When looking at each exposure across age groups (e.g. the effects of BMI in children, adolescents, young adults, and adults), we find highly similar effects in individuals measured at multiple time points (children, adolescents, and young adults). A similar metabolic profile is apparent in adults, though effect sizes appear slightly larger. The larger effects seen in adults may be due to the fact that metabolite concentrations have been shown to increase in older populations over time[137]. Given that longitudinal work has shown that BMI tracks over time[165,166] there may be a dose response relationship here whereby increased adiposity over time leads to increased metabolite concentrations.

Within each age group, there was high directional consistency across the three exposures. Effect sizes across exposures were similar within age groups, with overlapping confidence intervals; BMI showed a broadly higher effect on metabolites across age groups. Effects for BF appeared to be closer to, and crossed, the null more often than BMI and WHR. This may suggest that overall adipose mass in addition to detrimental deposition, may be driving the effect of increased adiposity on metabolites which may lead to disease.

These results are consistent across models; consistency in the direction of effect estimates were observed for the majority of tests. The effect size was broadly similar in the case of models 1 and 2. There was a decreases in effect sizes in model 3 compared with 1 and 2. However, confidence intervals overlapped across the majority of tests even if they crossed the null in some instances for model 3. Consistency across models suggests the association between measures of adiposity and metabolites shows weak evidence of confounding. Whether these results represent a true causal association or are subject to reverse causation or residual confounding requires further investigation.

Previous work by Wurtz et al. (2014)[149] identified numerous associations between BMI and metabolites in a large population. Results here are broadly in line with theirs in terms of effect direction. However, the size of effects differed drastically for a number of metabolites, with much larger effects seen in the study by Wurtz et al(2014)[149]; for the remaining metabolites effect sizes were comparable. These large differences may be a result of differences in metabolite data preparation; here, metabolomics data underwent quality control and if the same quality control had been eprformed by Wurtz et al. (2014)[149] some metabolites may have been excluded. Also, metabolites reported here are absolute values where as Wurtz et al. (2014)[149] scaled concentrations to standard deviation units. In addition, where as multiple covariates were included here, only age and sex were included by Wurtz et al. (2014)[149]. Though effect sizes differed there was consistency in effect direction for key metabolites such as phenylalanine and tyrosine, which, as a result of increased adiposity is increased across ages here and in numerous studies[167–174].

4.4.1 Limitations

Metabolomics

There is no standardised approach, nor a gold standard, for performing metabolomics quality control. Here, quality control, including outlier detection and removal, was performed using the `MetaboQC` `R` package. The default settings for exclusions based on metabolite missingness (20%), sample missingness (20%), total sum abundance (5 SD), and principal components (5 SD) were used. Most samples were removed for having missingness > 20% compared to total peak area and PC. Twenty percent sample missingness is arbitrarily defined and used among other studies[139], however a more stringent threshold (e.g. 5%) may have impacted on results. Especially given that metadata such as batch and runday information was not available. `MetaboQC` calculated the number of independent metabolites using a clustering dendorgram and a tree cut height based on a Spearman's Rho of 0.5. Although most metabolites were shared across age groups, differences in the number of independent metabolites were found. There were also differences in the number of clusters and truly independent metabolites. Similalry, inclusion of derived metabolites resulted in differing numbers of independent metabolites.

Data availability

Metabolomics measures were taken at specific time points in ALSPAC children and at ~50 years of age in adults. Though measures of adiposity were available at the same time points, data on confounders was not. Smoking status for example was available for adult males at the metabolomics clinic but the closest available measure for adult females was a number of years earlier, in which time they may have taken up smoking. Although data were obtained where available from the closest time point, the mismatch in timings may bias results, particularly in the case of smoking and alcohol consumption.

In all age groups, the availability of data was limiting. Absence of physical activity data meant model 3 was not performed for children, while absence of diet data in young adults and adults meant models 2 and 3 were constrained. However, adjusting for diet where available (children and adolescents) had little impact on results (Table 4.5) and is therefore likely not to have changed findings in young adults and adults.

In children, body fat percentage was not available. A raw impedance measure was available and derivation of BF using Equation (4.1) showed positive correlation with BMI and weight in children and BF measures in adolescents. However, this derived measure included numerous negative estimates of BF. The equation performed well in adolescents, correlating highly with DXA derived BF (Figure 4.3). The negative estimates of BF are likely a result of Equation (4.1) being derived in an adult population. Brief investigation showed negative estimates of BF remained when using adolescent age with child height and weight (data not shown). Given that in single frequency devices impedance is based on the volume of an individual it is probable that the values used in the equation do not accurately reflect the proportions of children pre-puberty. Child-specific equations were not available and the manufacturer was unwilling to share the equation used by their impedance devices. However, given that in a linear model the estimate is based on the per-unit increase, the absolute value negative or otherwise, will not impact on the final result.

Sensitivity analyses

The distribution of BMI at each age group was very similar across sexes. However, the distribution of WHR and BF differed among sexes in adolescents, young adults and adults; men had on average a higher WHR while women had a higher BF. Though Z-scores were used and sex was included as a covariate, the differences in WHR and BF distributions may highlight an underlying difference, which confounds the relationship between adiposity and metabolites. For example, hormonal contraceptive use has shown to influence the metabolome[175] and is not regularly taken by individuals with a high BMI[176]. There was little difference in results from the three models in regards to direction of effect estimates. However, when including only individuals with physical activity (model 3) the size of effects and the number of associations reaching a multiple testing threshold decreased. Given the consistency in the direction of effects across models and the highly similar effects across model 1 and 2 there is likely little effect of confounding. However, the possibility of unmeasured confounding can not be ruled out.

4.4.2 Summary

The large number of associations identified using multiple exposures adds weight to the evidence, shown previously for BMI, of association between increased adiposity and metabolites. As with previous work, we find associations between increased adiposity and many metabolites, including increased phenylalanine and tyrosine and decreased HDL components. This work highlights the large effects of increased adiposity on the global metabolic profile and shows that effects likely persist over time. Puberty is likely to have an affect on both adiposity, physical activity, and the metabolome and the lack of available data in children (BF and physical activity) means this requires further investigation, particularly as the adolescent time point used will have included post-pubertal individuals. Though confounders were taken into account the potential for unmeasured confounding is likely, and follow-up analysis will require this to be taken into account. Of particular note is the increasing effect size and number of associations as a result of increased adiposity across the metabolic profile with age. Given that many adiposity associated diseases occur later in life, exposure to an altered metabolic profile over time may be important in disease development, especially as weight loss in overweight and obese individuals is associated with reductions in elevated and increases in reduced metabolites[148].

Chapter 5

Mendelian randomization analysis

Associations between multiple measures of increased adiposity and metabolites: Mendelian randomization analysis

The large number of associations identified in Chapter 4 and previous observational studies are likely affected by residual confounding. As discussed in Chapter 1, methods which are somewhat robust to this issue, such as Mendelian randomization, provide an opportunity to further interrogate these associations. Consistent results between observational and Mendelian randomization analyses will strengthen evidence of association between increased adiposity and metabolites and may help to restrict the number of metabolites taken forward for subsequent disease analysis.

5.1 Introduction

The effects of increased adiposity are observed across the metabolome, with changes in the metabolic profile persisting after correction for measured confounders (Chapter 4). These persistent effects are similar to previous observational results[149].

Estimates from observational studies are likely impacted by resuidal confounding. This is also true of models which have been corrected for likely confounders. The effects of residual confounding can lead to larger than expected effect estimates. Bias away from the null is also a factor when reverse causation is present. Mendelian randomization, as discussed in Chapter 1 (1.6), is able to overcome some of the limitations present with observational studies[80].

Work in Chapter 4 is likely not to have fully accounted for confounding, either due to measurement error or unmeasured confounding. For instance, in adults physical activity was measured by questionnaire with possible answeres of ‘no’, ‘occassionally (less than monthly)’ and ‘frequently (once a month or more)’. Broad categories such as these are unlikely to capture the full impact of physical activity given that ‘frequently’ will encompass individuals who exercie once a month as well as every day. It also does not take into account the intensity of the exercise or its duration. Similar criticism can be placed on the included confounders smoking status and frequency of alcohol consumption. The presene of reverse causation can also not be ruled out. It is possible that metabolic changes promote increased adiposity, though this may be a result of other factors such as diseased states.

With large publicly available GWAS data on metabolites and measures of increased adiposity, here MR is used to examine the causal effect of increased adiposity on the metabolic profile. Particular focus is given to associations which are consistent with those observed in Chapter 1.

5.2 Methods

This chapter details a hypothesis-free two-sample summary-level MR analysis using SNPs for three measures of increased adiposity (BMI, WHR, and BF) measured in individuals of European ancestries as exposures. Outcomes across the three exposures consisted of 123 NMR derived metabolites measured in individuals of European ancestries. The main analysis consisted of an inverse variance weighted multiplicative random effects (IVW-MRE) model and sensitivity analyses using additional models (Figure (5.1).

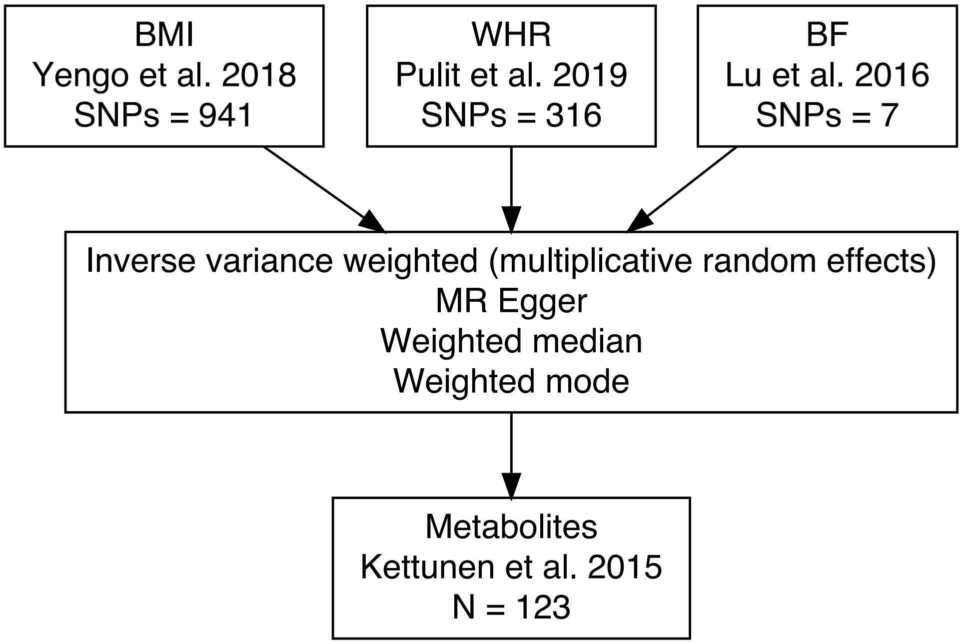

Figure 5.1: Schematic of Chapter 5 main analysis

The main analysis in chapter 5 included three exposures (BMI (body mass index), WHR (wasit hip ratio), BF (body fat percentage)), 4 models, and 123 metabolite outcomes. The number of SNPs used for each exposure is given alongside the reference for the studies in which the summary data were obtained. The inverse variance weighted, multiplicative random effects model was the main analysis MR Egger, weighted median, and weighted mode are additional sensitivity analyses.

5.2.1 Outcomes: metabolites

Genome-wide summary level data for 123 NMR derived metabolites (Supplementary Table A.4) were obtained from Kettunen et al. (2016)[125] from MR Base[177].

Kettunen et al (2016)[125] performed a fixed effects meta-analysis of 123 serum and EDTA serum NMR quantified metabolites from 14 GWASs. In total, up to 24,925 (men = 11,245; women = 13,680) individuals of European ancestries were included in the meta-analysis. A total of 62 SNPs reached a genome wide significance threshold (*p-value* $< 2.27 \times 10^{-9}$) after correcting for 22 independent tests (22 being the number of principal components explaining over 95% of variation in the metabolite data). After performing conditional analysis, a further 12 SNPs were identified as independent after reaching the genome-wide significance threshold. The 12 additional SNPs were identified in 9 of the 62 main loci (*PCSK9*, *LPL*, *PPM1K*, *HAL*, *CETP*, *CILP*, *PLTP*, *APOB* and *LIPC*), with a third independent SNP identified in two of these loci (*APOB* and *LIPC*) and a fourth independent SNP identified in one of these (*LIPC*). Overall, 74 independent SNPs were associated with one or more of the 123 metabolites, with the variance explained ranging from 0.2% for acetoacetate to 12.5% for glycine, with a median of 5%.

For the independent GWASs, in each of the 14 cohorts 123 Metabolites were quantified from human blood. Four cohorts used EDTA-plasma, the other 10 used serum. The majority of blood samples were fasted. Where a study did not have over night fasted samples correction for fasting time effect was performed using the `gam` R package and fitting a smoothed spline to adjust for fasting. The NMR analysis was performed with the comprehensive quantitative serum/plasma platform described by Soininen et al. (2009)[151]. All metabolites were first adjusted for age, sex, time from last meal if applicable, and the first ten genomic principal components. The residuals were inverse rank normally transformed. Each of the 14 cohorts performed a univariate GWAS assuming an additive genetic model. SNPs were imputed up to 39 million markers using the 1000 Genomes Project March 2012 version.

For the meta-analysis, SNPs with accurate imputation (info > 0.4) and minor allele count > 3 were combined using double genomic correction, that is, both individual cohort results and meta-analysis results were corrected for the genomic inflation factor as implemented in `GWAMA`. Up to 12,133,295 SNPs were included in the meta-analysis. Variants, after filtering and meta-analysis, present in more than seven studies were considered for the final results. All traits gave genomic inflation factors in the meta-analysis less than 1.034 showing little evidence of systematic bias in the test statistic.

5.2.2 Exposures: measures of increased adiposity

Genetic instruments were obtained separately for each of three exposures (BMI, WHR, BF). In each case, the following data was obtained: SNP (rsID), effect allele, other allele, effect allele frequency, beta, standard error, *p-value*. F statistics were calculated for each SNP and a mean taken for each exposure – a nominal threshold of 10 was set.

Body mass index

Genetic instrumental variables for BMI were extracted from Yengo et al. (2018)[98], who analysed data from 515,509 — 795,624 individuals of European ancestries from two studies, the Genetic Investigation of Anthropometric Traits (GIANT)[96] and UK Biobank. In both studies BMI was calculated as $\frac{weight\ (kg)}{height\ (m^2)}$. Yengo et al. (2018)[98] performed a fixed effect inverse variance weighted meta-analysis of BMI using GWAS results generated from UK Biobank (N = 456,426) and results from the GIANT consortium, Locek et al. (2015)[96].

In UK Biobank, BMI was adjusted for age, sex, recruitment centre, genotyping batch, and the first 10 principal components calculated from 132,102 (out of 147,604) genotyped SNPs pre-selected by the UK Biobank quality control team[178]. In GIANT, BMI was adjusted for age, age squared, and study specific covariates. Both the UK Biobank and GIANT GWASs inverse normally transformed BMI. In total, 681,275 individuals of European ancestry and ~2.4 million HapMap 2 SNPs were included in the meta-analysis. Linkage disequilibrium score regression (ILDSC 1.03; SE = 0.02) suggested population stratification, however LDSC can rise above 1 as sample sizes and heterogeneity increase[179].

In the combined meta-analysis, a total of 656 primary associations reaching a genome wide significance threshold of 5×10^{-8} were identified. Approximate conditional and joint multiple-SNP (COJO) analysis identified a further 285 independent SNPs reaching a genome-wide significance threshold (*p-value* $< 1 \times 10^{-8}$). Together these 941 associations explain 6% (SE = 0.8%) and 22.4% (SE = 3.7%) of the variance and heritability of BMI respectively. COJO specific summary statistics for all 941 SNPs were used in the main analysis.

Waist hip ratio

Genetic instrumental variables for WHR were extracted from Pulit et al. (2019)[97], who analysed data from 485,486 — 697,702 individuals of European ancestries from two studies, UK Biobank and GIANT, Shungin et al. (2015)[95]. In both studies WHR was calculated as $\frac{waist\ circumference\ (cm)}{hip\ circumference\ (cm)}$. Pulit et al. (2019)[97] performed a fixed effects inverse variance weighted meta-analysis of WHR using GWAS results generated from UK Biobank (N = 485,486 (men = 263,148; women

= 222,338)) and results from the GIANT consortium (N = 212,248 (women = 118,004; men = 94,434))[95] using METAL[180]. SNPs with a frequency difference > 15% between the two studies were removed prior to meta-analysis. In both studies, WHR was adjusted for sex (UK Biobank only), age at assessment, age at assessment squared and assessment centre (UK Biobank only); study specific covariates were included in the GIANT GWASs where appropriate. All residuals were inverse rank normally transformed; in GIANT residuals were calculated for men and women separately. In total, 316 associations reaching a genome wide significance threshold of 5 x 10^{-9} were identified; *p-value* adjusted to account for denser imputation data[181]. These associations explain 3% of the phenotypic variance as calculated in an independent dataset (N = 7,721). SNP based heritability across all SNPs was estimated to be 22.7%.

For the UK Biobank GWAS the second release (June 2017) of UK Biobank data which did not have corrected imputation at non-HRC sites was used. As such, only HRC SNPs were used in the GWAS. A linear mixed model using BOLT-LMM[182] was performed on SNPs with imputation quality score > 0.3, MAF > 0.01% and SNPs present in the HRC imputation reference panel. Adjustment was made for the SNP array used to genotype the sample. No other covariates were used. They did not assume a non-infinitesimal model. In GIANT, individual studies (genome-wide array = 57; Metabochip = 44) recruited participants and undertook sample and SNP quality control. In genome-wide array studies, imputation was performed with CEU haplotypes from HapMap. Assuming an additive genetic model, each study ran a linear regression GWAS. Sex-specific summary statistics were corrected for population structure using the genomic control inflation factor. Prior to meta-analysis of genome-wide array studies and Metabochip studies, SNPs were removed if they had a minor allele count <= 3, were not in Hardy-

Weinberg equilibrium (*p-value* < 10^{-6}), had a call rate < 95% or an imputation quality score < 0.3 for MACH, 0.4 for IMPUTE, and 0.8 for PLINK. A fixed effects inverse variance weighted meta-analysis of each genome-wide array GWAS and each Metabochip GWAS was performed and corrected for genomic control to account for structure between cohorts. A fixed effects inverse variance weighted meta-analysis of the meta-analysed genome-wide array studies and Metabochip studies was performed using METAL; correction for genomic control was not performed.

Body fat percentage

Genetic instrumental variables for BF were extracted from Lu et al. (2016)[183]. This was the only available GWAS using DXA as a measure of BF (as of 25/07/2019); the number of individuals with DXA measures was not reported. Lu et al. (2016)[183] performed a fixed effects inverse variance weighted meta-analysis of BF using two meta-analyses generated from 43 GWASs (N = 65,831) and 13 Metabochip GWAS studies (N = 23,468) using METAL[180]. In total, up to 89,300 (men = 44,429; women = 45,525) individuals of European ancestries were included in the inverse variance weighted fixed effects meta-analysis. In total 7 SNPs reached a genome wide significance threshold (*p-value* < 5 x 10-8) and were considered independent (± 500kb of the most significant SNP). Estimation of variance explained was not available in the European ancestries meta-analysis. In the all ancestries meta-analysis, which included up to 11,419 additional individuals of non-European ancestries, these 7 SNPs explained 0.416% of the variance in BF – additional SNPs identified in the all ancestries meta-analysis explained 0.58% of the variance in BF.

In each cohort, BF was measured via a bioletrical impedance device or DXA as described previously[184]. For each study, BF was adjusted for age, age squared and study-specific covariates (e.g. genotype-based principle components and study centre), if necessary. For studies of unrelated individuals, the residuals were calculated separately in men and women, and in cases and controls. For studies of family-based design, the residuals were calculated in men and women together, and sex was additionally adjusted in the model. The residuals were then inverse rank normally transformed for association testing. For studies of family-based design, the family relatedness was additionally adjusted in the association testing.

Meta-analysis was performed in two stages. First, two parallel meta-analyses were conducted; one meta-analysis combined summary statistics from 43 GWASs, totalling up to 65,831 individuals of European ancestries and the other meta-analysis combined summary statistics from 13 Metabochip studies, totalling up to 23,469 individuals of European ancestries. Each study performed study specific quality control. Imputation was performed in each study using the European ancestries HapMap Phase II (Release 22) reference panel. Individual SNPs were associated with inverse normally transformed BF residuals using linear regression with an additive model. All SNPs with low imputation scores (MACH r2-hat < 0.3, IMPUTE proper_info < 0.4, or PLINK info < 0.8) and a MAC <= 3 were removed. The `EasyQC` software was used for detailed QC of study level analyses and meta-level analysis.

In the second stage, a single meta-analysis of the GWAS meta-analysis results and the Metabochip meta-analysis results was performed. This included up to 89,300 individuals of European ancestries from 56 studies. Meta-analysis was performed using an inverse variance-weighted fixed-effect method using METAL. Inflation before genomic control correction was generally low (lambda men + women = 1.13; lambda men = 1.07; lambda women = 1.10). To reduce inflation of test statistics from potential population structure, individual GWAS results and GWAS meta-analysis results were corrected for genomic control using all SNPs. Individual Metabochip results and Metabochip meta-analysis results were genomic control corrected using 4,425 SNPs, which were derived from pruning of QT-interval replication SNPs within 500 kb of an anthropometry replication SNP on the Metabochip. The genomic control corrected GWAS and Metabochip meta-analysis results were then meta-analysed.

LDSC suggested observed inflation was not due to population substructure; the regression intercept was 1.0045 (lambda genomic control = 1.136 and mean X2 = 1.16) for sex-combined, 0.999 (lambda genomic control = 1.062 and mean X2 = 1.079) for men-only and 1.014 (lambda genomic control = 1.105 and mean X2 = 1.112) for women-only analyses. The authors used these regression intercepts, rather than the lambda genomic control, to correct the meta-analysis results in more significant associations (for example, for the rs1558902-*FTO* SNP, *p-value* = 3.24 x 10-27 in the modified European sex-combined meta-analysis compared with *p-value* = 1.1 x 10-25). Overall, the less stringent correction did not result in the identification of novel loci.

Each unique locus was defined as ±500*kb* on either side of the most significant SNP that reached the genome wide significance threshold (*p-value* < 5 x 10-8) in the meta-analysis. Genotype data for genome-wide significant SNPs was of high quality with a median imputation score of >= 0.95. The fifth percentile for all SNPs was >= 0.80, except for the previously established *TOMM40* SNP (P5 = 0.52).

5.2.3 Statistical analysis

All data manipulation and analysss was perfromed using `R`[146] (version 3.5.3). MR analysis was performed using the `TwoSampleMR`[177] (version 0.4.22) `R` package. Data on metabolites were obtained from MR Base (accessed 26/07/2019).

For all exposures, the following data were obtained from the original GWAS publications: rsID, effect allele, other/non-effect allele, effect allele frequency, effect estimate, standard error of the effect estimate, *p-value*, N, and units. The same data for these genetic instrumental variables were obtained from each metabolite for each exposure separately. Where genetic instrumental variables were not present in the metabolite GWASs, proxy SNPs were included if linkage disequilibrium was >= 0.8. For proxy SNPs, the inclusion of SNPs where the reference strand was ambiguous (strand flips) was allowed and the direction was inferred using a minor allele frequency threshold of 0.3.

Exposure and outcome SNPs were harmonized in reference to the exposure effect allele being on the increasing scale. For included alleles where the reference strand was ambiguous, the positive strand was inferred using effect allele frequency.

Main analysis

An inverse variance weighted (IVW), multiplicative random effects (IVW-MRE) model was used to investigate the causal association of each exposure on each metabolite. The model assumes that the strength of the association of the genetic instruments with the exposure is not correlated with the magnitude of the pleiotropic effects and that the pleiotropic effects have an average value of zero[185]. A multiple testing threshold of *p-value* < 0.0022727 was used. This is based on the number of principal components (22) in the Kettunen et al. (2016)[125] meta-analysis that explained 95% of the variation in metabolite data. Consistency in the direction of effect estimates was investigated and Spearman's Rho analysis of effect estimates was performed.

For the main analysis, results represent the change in the inverse rank position of each metabolite per change in the inverse rank position of the exposure.

Sensitivity analysis

Assumptions of no pleiotropy among genetic instruments and outcomes were explored using MR-Egger[186], weighted median[187] and weighted mode[188] based estimators, which are sensitive to the effects of potential pleiotropy. No threshold requirements were set for these methods, instead consistency between the IVW-MRE model and these methods was investigated.

MR-Egger provides an estimate of horizontal pleiotropy via the intercept of a linear regression of the SNP-exposure and SNP-outcome association. Absent pleiotropic effects the intercept tends towards the origin. MR-Egger gives consistent estimates when 100% of genetic instruments are invalid[186]. The weighted median is complimentary to MR-Egger but does not rely on the instrument strength independent of direct effect assumption. It calculates the median of an empirical distribution of effect estimates weighted for precision. It provides consistent estimates when at least 50% of the weight comes from genetic instruments and as long as no one genetic instrument contributes > 50% of the weight[187]. The weighted mode assumes the true causal effect is the most common effect. It relies on the assumption that across all instruments the mode is 0[188].

The effects of heterogeniety in the exposure instruments was investigated using Cochrane's Q statistic for maximum likelihood, IVW, and MR Egger models. A single SNP MR, whereby the causal association of each SNP individually is estimated using the maximum likelihood and Wald ratio models, was also used to investigate heterogeneity. A leave-one-out MR analysis was performed whereby each SNP is sequentially left out of the MR analysis and the causal effect estimated absent of that SNP. If the estimated effect is substantially reduced after the removal of a single SNP this may imply violation of the exclusion restriction assumption and that this SNP is having a direct association with the outcome that is not mediated through the exposure. Finally, each of these additional sensitivity analyses were visualised using a funnel plot of the instrument beta and standard error and using forest plots of the single SNP and leave-one-out MR analysis to identify potential pleiotropic effects. Additional sensitivity analysis is presented as a summary for each exposure. Where appropriate, i.e. for results which appear to be strong associations, specific results are discussed.

5.2.4 Additional analyses

In the main analysis both BMI and WHR genetic instrumental variables were obtained from studies using UK Biobank, which has shown evidence of latent population structure[89,90] (See 1.6). Additionally, BMI instruments were obtained from a COJO analysis, which, as these SNPs are conditional on the presence of an independent SNP, may lead to potential pleiotropic pathways. Finally, BF instruments were obtained from a study which used different measures of BF; two of the included SNPs have also been associated previously with 'favourable adiposity' and may therefore not be reflections of total body fat[189,190]. In order to test whether genetic instrumental variables in the main analysis produced biased results a two step additional analysis was performed.

Firstly, genetic instrumental variables for BMI, WHR and BF were obtained from additional sources (Supplementary Table A.5). Outcome data extraction and harmonization was performed as for the main analysis. F statistics and detailed information on each additional exposure is available in Supplementary information. Briefly, SNPs for BMI were obtained from the initial non-COJO analysis by Yengo et al 2018[98], and a separate set of SNPs were obtained from Locke et al. (2015)[96] which did not use UK Biobank; for WHR, SNPs were obtained from Shungin et al. (2015)[95] which did not use UK Biobank; for BF, the SNPs associated with 'favourable adiposity' were removed and an additional SNP set identified in a GWAS using a single measure of BF was obtained from Hubel et al. (2019)[191].

In stage one, the main analysis (IVW-MRE, MR-Egger, Weighted median, Weighted mode and additional sensitivity analysis) was performed using these additional exposures. In stage two, genetic instrumental variables for all exposures (those used in the main analysis and in additional analyses described here) were clumped and the main analysis was performed. Clumping was performed using the `R` package `TwoSampleMR`[177] (version 0.4.22) setting a linkage disequilibrium R^2 threshold of 0.001 for SNPs within a 10,000 base window of each other. Spearman's Correlation between MR results from the non-clumped and clumped SNP lists was performed.

5.2.5 Comparison with observational estimates

Finally, comparison of results here and those from observational analysis conducted in Chapter 4 was performed. Observational estimates from the adult analysis, adjusted for age and sex, were used along with those of the main analysis here. Firstly, consistency in the direction of effect within exposures across MR and observational estimates was investigated, and a Spearmans Rho analysis was performed. Secondly, tests reaching a multiple testing threshold across both observational and MR analyses within exposures were investigated. Finally, tests which showed consistency in direction of effect and which reached a multiple testing threshold across analyses and exposures were investigated.

5.2.6 Comparison with Wurtz et al. (2014)[149]

5.3 Results

5.3.1 Main analysis F-statistics

Numerous SNPs were used for each exposure in the main analysis. For each SNP an F-statistic was calculated and a mean taken for each exposure. Across all three exposures, no single SNP had an F-statistic less than 10. Mean F-statistics: BMI = 73, WHR = 66, BF = 44 (Figure 5.2).

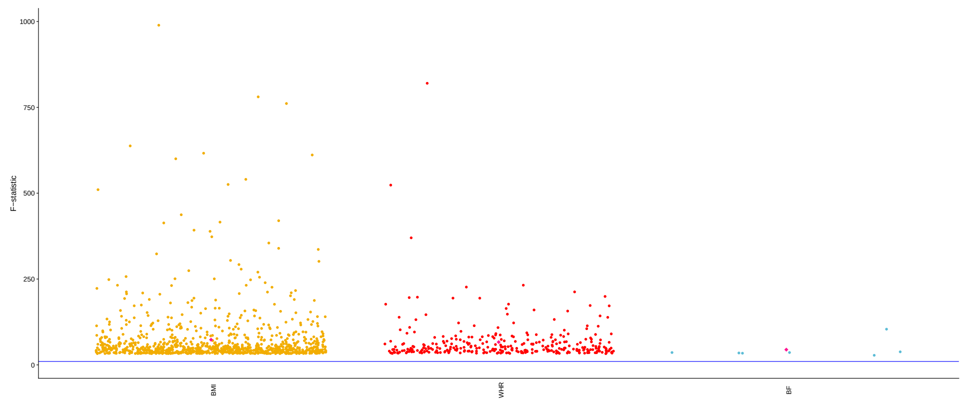

Figure 5.2: Main MR analysis f-statistics

Mean f-statistics for each exposure indicated by the pink diamond. The blue line indicates a nominal threshold of 10. BMI = body mass index, WHR = wasit hip ratio, BF = body fat percentage.

5.3.2 Statistical analysis

Main analysis

Directional consistency Across all three exposures, directional consistency was low (Figure 5.3), with over 100 of the 123 tests showing an opposite direction of effect for at least one exposure. Consistency in the direction of effect was highest for BMI and WHR, where a mjority of tests showed positive effects. Directional inconsistency was largely due to BF having an opposite direction of effect on metabolites to BMI and WHR. Spearman's Rho analysis of effect estimates showed a positive correlation between BMI and WHR (R^2 = 0.94), while negative correlations were observed for BF and BMI (R^2 = -0.70) and BF and WHR (R^2 = -0.72) (Supplement

A.4.3).

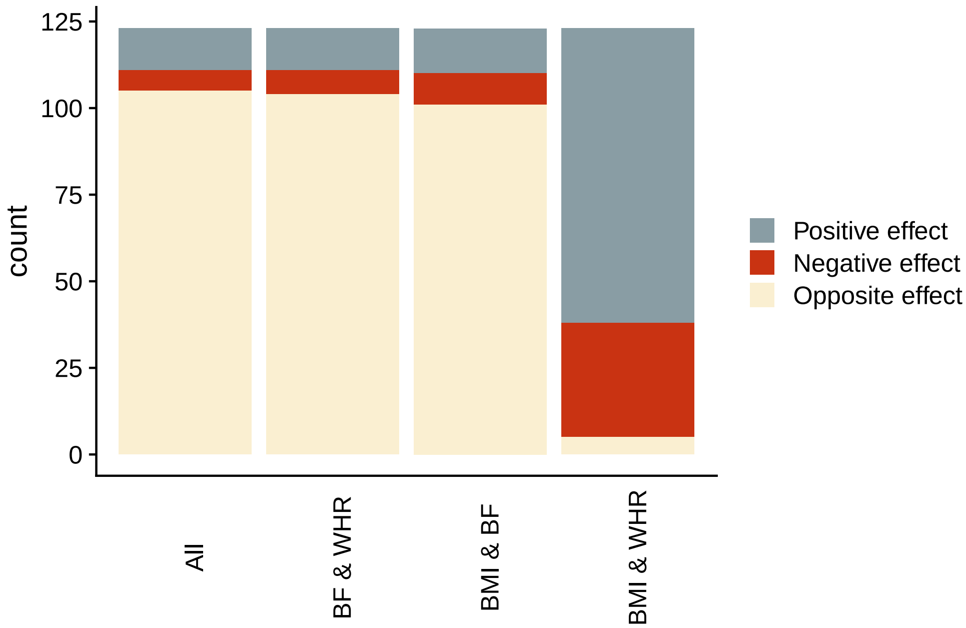

Figure 5.3: Directional consistency across exposures

Figure 5.3 shows the directional consistency of all exposures from the main analysis: BMI (Yengo et al. (2018)), WHR (Pulit et al. (2018)), BF (Lu et al. (2016)). A positive effect reflects the effect estimate from two or more exposures being in the positive direction; a negative effect reflects betas being in a negative direction; opposite effect reflects different directions for the effect estimates. BMI = body mass index; WHR = waist hip ratio; BF = body fat percentage.

Multiple testing threshold A total of 63, 63, and 0 tests reached a multiple testing threshold for BMI, WHR and BF respectively. Of these tests, 58 reached a multiple testing threshold across both BMI and WHR. A total of 5 and 5 tests reached a multiple testing threshold for BMI only and WHR only respectively. For

BMI, these metabolites included, Acetate (mmol/l), Average number of methylene groups per double bond, Concentration of IDL particles (mol/l), Monounsaturated fatty acids; 16:1, 18:1 (mmol/l), Phospholipids in very small VLDL (mmol/l); for WHR, these metabolites included, Glutamine (mmol/l), Lactate (mmol/l), Concentration of small HDL particles (mol/l), Total cholesterol in very large HDL (mmol/l), Cholesterol esters in very large HDL (mmol/l).

Given no tests reached a multiple testing threshold for BF, focus here is on the tests reaching a multiple testing threshold across both BMI and WHR. All tests reaching the multiple testing threshold for BMI and WHR where directionally consistent across BMI and WHR (Figure 5.4). Of the tests which reached a multiple testing threshold across BMI and WHR, 4 were directionally consistent across BMI, WHR and BF, with positive effect estimates for: Phenylalanine (mmol/l), Tyrosine (mmol/l), Valine (mmol/l); and negetive effect estimates for Apolipoprotein A-I (g/l) (Figure 5.5. Effect sizes were broadly consistent across BMI and WHR; BF had much larger confidence intervals which spanned the null.

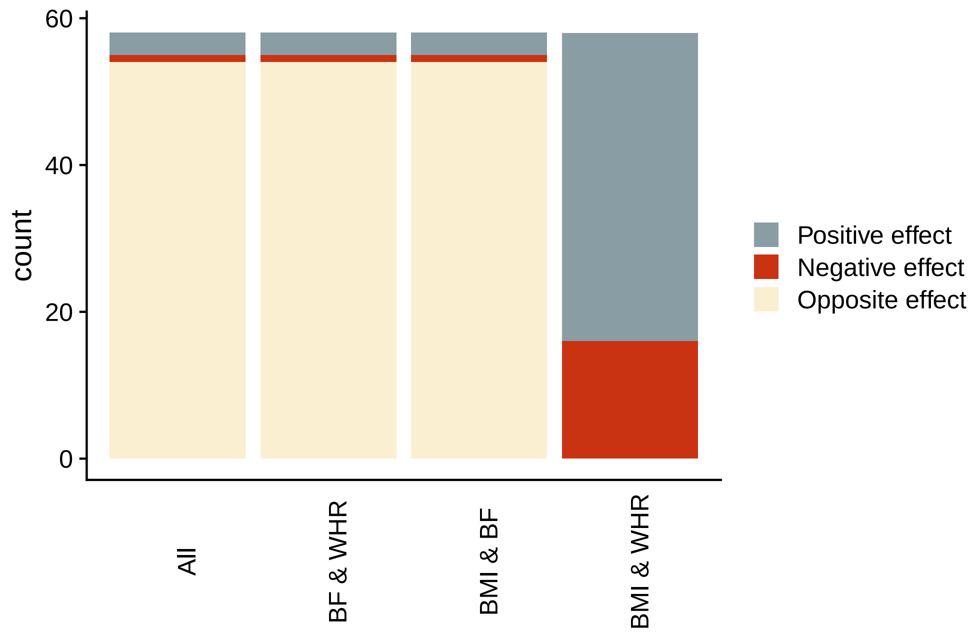

Figure 5.4: Directional consistency across exposures for tests reahcing a multiple testing threshold

Figure 5.4 shows the directional consistency of all exposures from the main analysis which reached a multiple testing threshold (p < 0.05/22): BMI (Yengo et al. (2018)), WHR (Pulit et al. (2018)), BF (Lu et al. (2016)). A positive effect reflects the effect estimate from two or more exposures being in the positive direction; a negative effect reflects betas being in a negative direction; opposite effect reflects different directions for the effect estimates. BMI = body mass index; WHR = waist hip ratio; BF = body fat percentage.

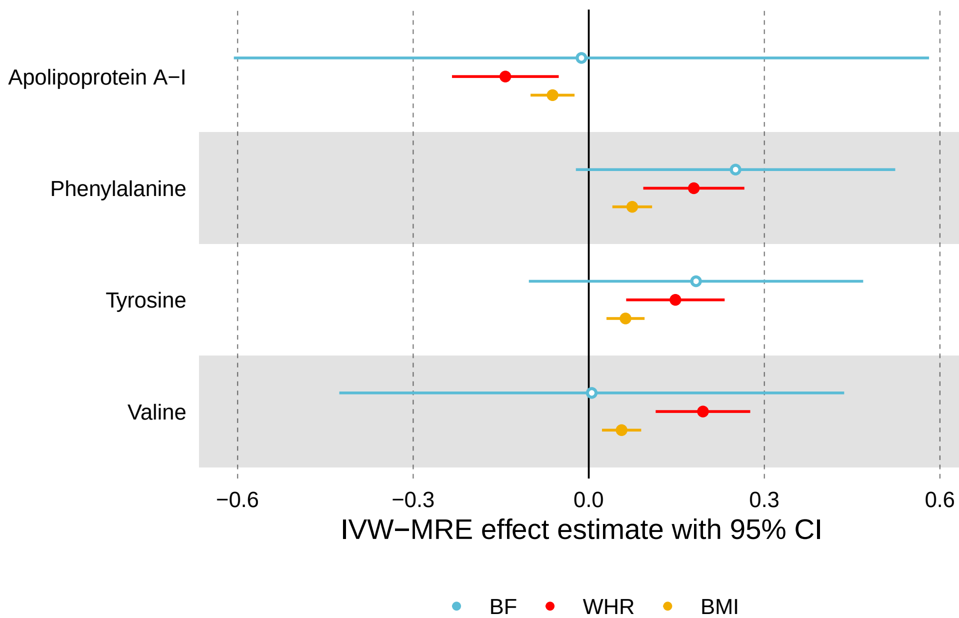

Figure 5.5: Forestplot of directionally consistent tests reaching a multiple testing threshold

Figure 5.5 shows effect estimates and 95% confidence intervals for the 4 metabolites which reached a multiple testing threshold (p < 0.05/22) for BMI and WHR and which where directionally consistent across all 3 exposures: BMI (Yengo et al. (2018)), WHR (Pulit et al. (2018)), BF (Lu et al. (2016)). Effect estimates represent the change in the inverse rank position of each metabolite per change in the inverse rank position of the exposure.

Global metabolic profile Globally, the pattern of association was visually very similar for BMI and WHR. Effects for WHR were generally larger with wider confidence intervals, whereas those for BMI where smaller with tighter confidnece intervals. Effects for BF were much larger with wide confidence intervals which spanned the null (Figure 5.6). The largest negative effects (> -0.75) were found for BF and the Total lipis and Particle concentration metabolites within the *Small LDL*, *Small VLDL*, and *Medium LDL* subclasses. The largest positive effects (> 0.40) were observed for BF and the *Medium HDL* and *Large HDL* subclasses. All metabolites in subclasses *Small VLDL*, *Medium VLDL*, *Large VLDL*, *Very large VLDL*, *Extremely large VLDL*, *Large HDL*, *Apolipoproteins*, *Branched-chain amino acids*, and *Aromatic amino acids* reached the multiple testing threshold across both BMI and WHR. In addition, metabolites in these subclasses all shared the same direction of effect with other metabolites within their respective subclass for both BMI and WHR.

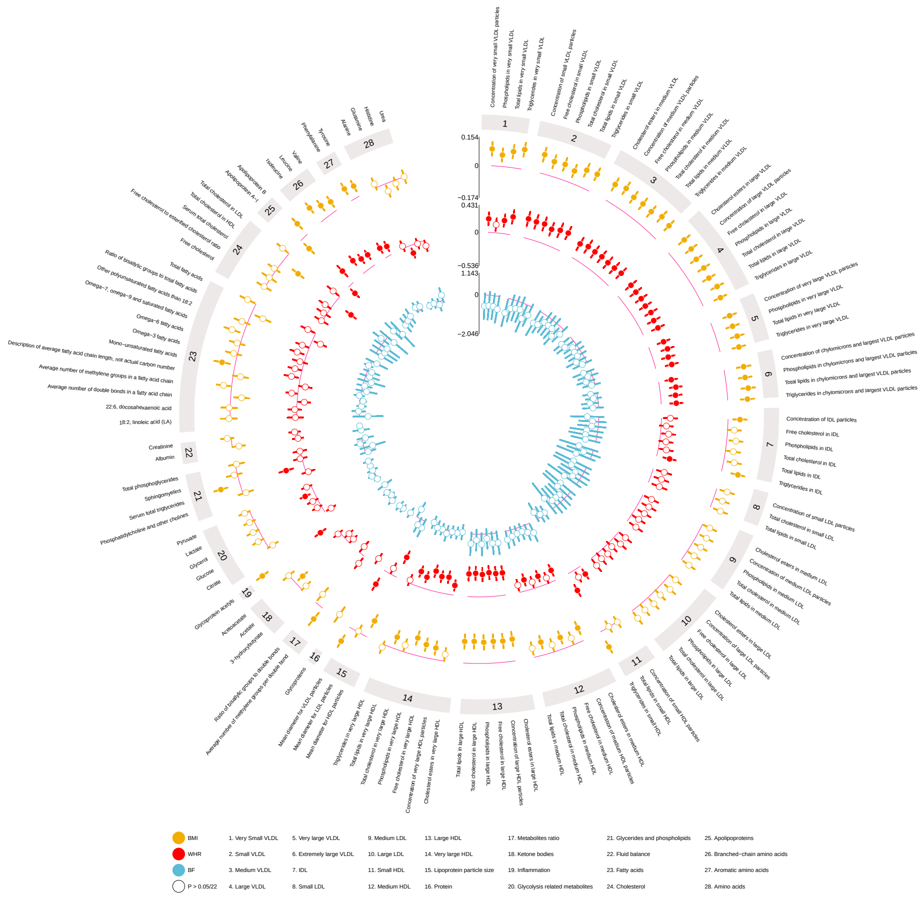

Figure 5.6: Circos plot of IVW-MRE effect estimates for BMI, WHR, and BF on 123 NRM derived metabolites

Figure 5.6 shows each track as one of the measures of increased adiposity; the outer track is BMI, the middle track is WHR, the inner track is BF. Solid points indicate a multiple testing threshold ($0.05/22$) *has been reached. Effect estimates represent the change in the inverse rank position of each metabolite per change in the inverse rank position of the exposure. 95% confidence intervals shown. Metabolites are grouped by subclass.*

Subclass results Tests reaching the multiple testing threshold were observed for at least one exposure in 23 of 28 subclasses. No tests reached a multiple testing threshold for subclasses: *Small LDL*, *Medium LDL*, *Large LDL*, *Protein*, *Fluid balance*. For subclasses *IDL*, *Metabolites ratio*, *Ketone bodies*, *Glycolysis related metabolites*, *Glycerides and phospholipids*, *Cholesterol*, and *Amino acids* only a small number of metabolites within each subclass reached the multiple testing threshold. Whereas, for subclasses *Small VLDL*, *Medium VLDL*, *Large VLDL*, *Very large VLDL*, *Extremely large VLDL*, *Large HDL*, *Very large HDL*, *Lipoprotein particle size*, *Branched-chain amino acids*, and *Aromatic amino acids* a majority of metabolites reached the multiple testing threshold (Figure 5.7).

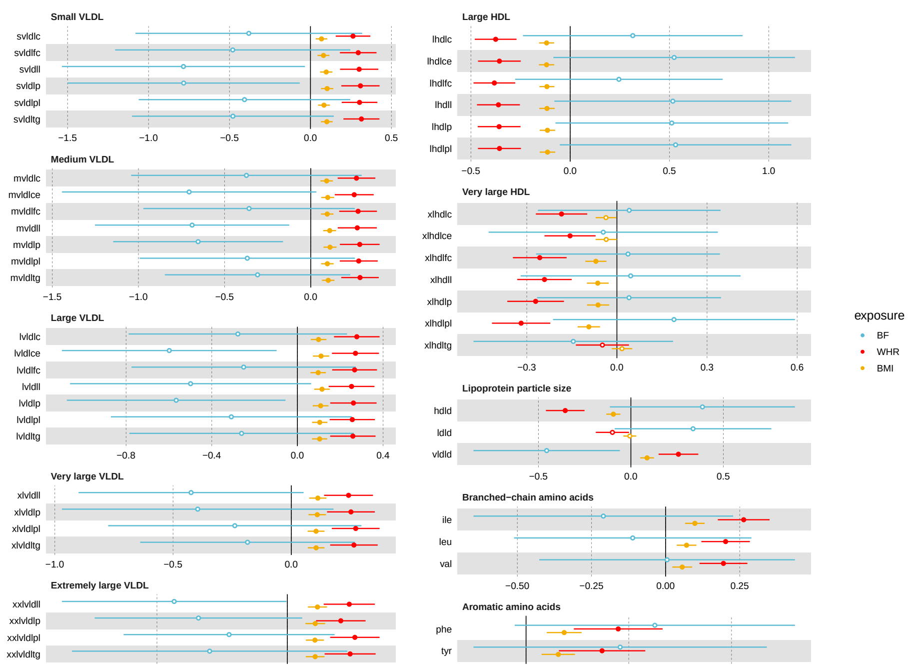

Figure 5.7: Forestplot of effect estimates across subclasses with a majority of metabolites reaching a multiple testing threshold for BMI and WHR

Figure 5.7 gives effect estimates and 95% confidence interval for all sublcasses in which the majority of metabolites reached a multiple testing threshold across BMI and WHR. Solid points reflect the multiple testing threshold (p < 0.05/22) has been reached.

Sensitivity analysis The majority of effect estimates for each metabolite showed directional consistency across the main analysis (IVW-MRE) and three models (MR-Egger, weighted median, weighted mode) used for sensitivity analysis for BMI (N = 69) and WHR (N = 98); BF showed the lowest directional concordance between models (N = 48; Figure 5.8). Of these directionally consistent tests within exposures and across methods, a total of 29 were directionally consistent across methods for all three exposures (Figure 5.9 - direction of effect for BF was on the whole opposite to BMI and WHR for all methods. Of these 29, only *Valine* was also found to be directionally consistent and reached a multiple testing threshold for both BMI and WHR in the main analysis (Figure 5.5. Globally, sensitivity analysis was visually reflective of the main analysis for each exposure, though with wider confidnece intervals (Supplementary Figures A.9, A.10, A.11). Confidence intervals for sensitivity analyses tended to cross the null and were widest for MR Egger. Sensitivity results for WHR appeared to show most consistency with the main analysis; confidence intervals for weighted median and mode models did not cross the null in a majority of results for subclasses: *Very Small VLDL*, *Small VLDL*, *Medium VLDL*, *Large VLDL*, *Very large VLDL*, *Extremely large VLDL*, *IDL*, *Small LDL*, *Medium LDL*, *Large LDL*, *Small HDL*, *Medium HDL*, *Large HDL*, *Very large HDL* (Supplemetary FIgure A.10).

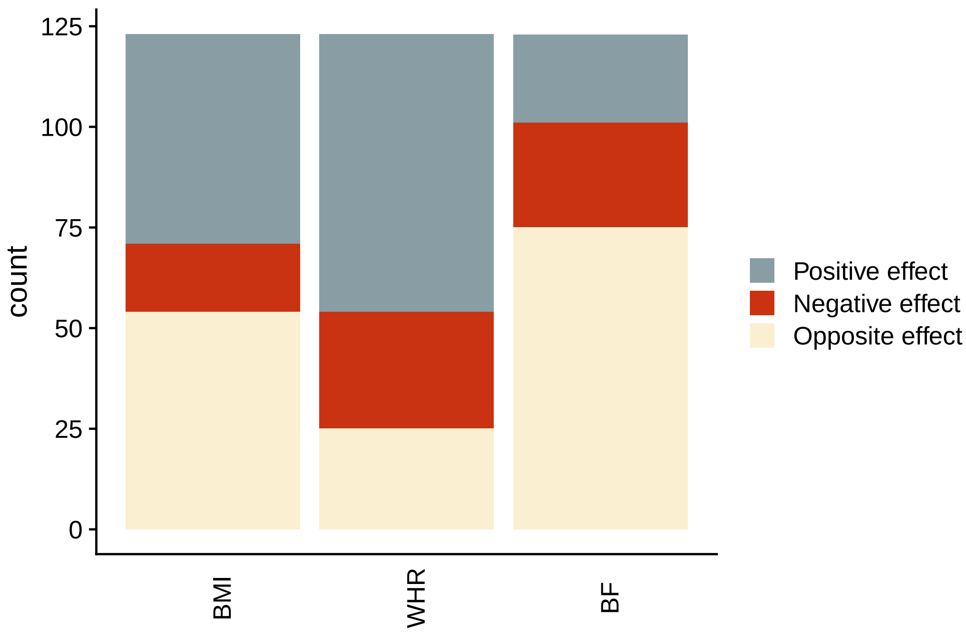

Figure 5.8: Directional consistency across MR models for each exposure

Directional consistency of all exposures from the main analysis: BMI (Yengo et al. (2018)), WHR (Pulit et al. (2018)), BF (Lu et al. (2016)). A positive effect reflects the effect estimate from two or more exposures being in the positive direction; a negative effect reflects betas being in a negative direction; opposite effect reflects different directions for the effect estimates. BMI = body mass index; WHR = waist hip ratio; BF = body fat percentage.

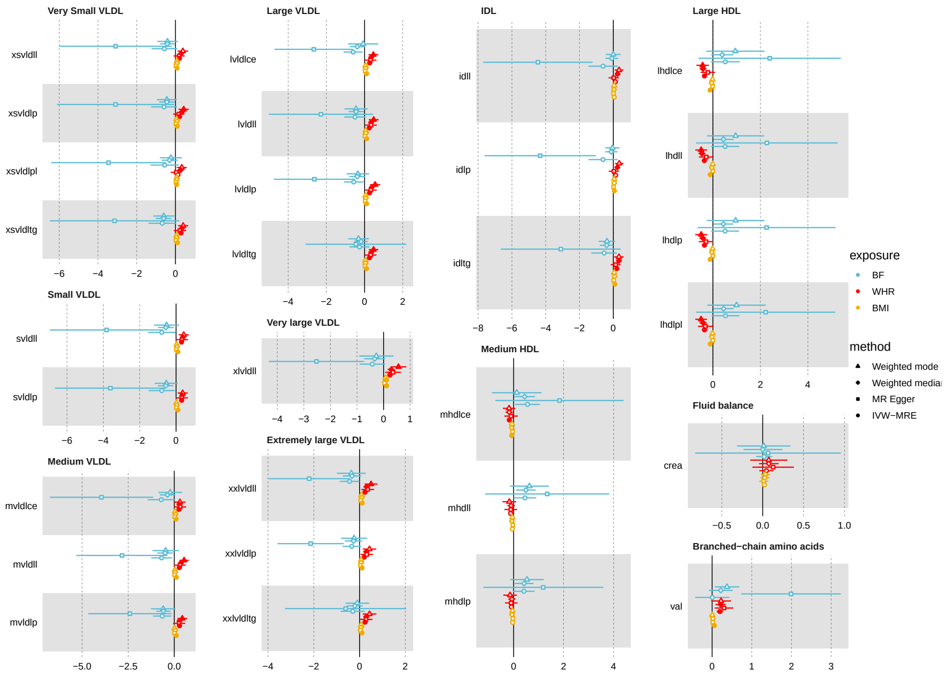

Figure 5.9: Forestplot of directionally consistent results across methods within exposures

Effect estimates and 95% confidence intervals for metabolites which showed diectionally consistent results across the main (IVW-MRE = inverse variance weighted multiplicative random effects) and sensitivity analysis (MR-Egger, weighted median, weighted mode) within each exposure. Of the directionally consistent results within exposures, a total of 29 were identified within all three exposures and are presented here. BMI = body mass idnex (Yengo et al. (2018)); WHR = waist hip ratio (Pulit et al. (2018)); BF = body fat percentage (Lu et al. (2016)).

Heterogeneity of the genetic instruments for each exposure, measured using Cochrane's Q statistic, was greater than the degrees of freedom for a majority of metabolites for all three exposures (Table 5.1). *The number of tests (exposure on*

Table 5.1: Number of tests in which Cochrane's Q exceeds genetic instrumental variable degrees of freedom

	ML	IVW	MR Egger
BMI	120	120	120
WHR	121	121	121
BF	112	111	112

metabolite) for which Cochrane's Q statistic exceeded the degrees of freedom (number of SNPs - 1) for each exposure. ML = maximum likelihood method, IVW = Inverse variance weighte dmethod; BMI = body mass idnex, WHR = waist hip ratio, BF = body fat percentage.

In single SNP MR analysis, visual inspection of forest plots showed characteristcly S shaped distributions of effect estimates for all tests (Representative Figure A.12; all figures GitHub). Funnel plots for BMI and WHR highlighted a number of SNPs lying outside of the funnel distribution which were investigated further (Representative Figure A.13 - the low number of SNPs used for BF did not result in meaningfully interpretable funnel plots (Representative Figure A.13. Effect estimates for some SNPs in the single SNP MR analysis appeared to be outliers, for example for BMI, rs4673553 showed a disproprotinately larger effect estimate of 22 (standard error = 0.85; *p-value* = 5.66 x 10^{-148}) for Glycoproteins when compared to other SNPs. Additionally, rs7777102 showed a disproprotinately larger effect estimate of -9 for Mean diameter for VLDL particles (standard error = 1.14; *p-value* = 6.15 x 10^{-17}). Looking at the median effect size across all metabolites for each SNP, a number of SNPs (including rs7777102 for BMI) showed dispraportionately larger median effect sizes. The number of SNPs with median effect estimates at the extremes (5% and 95%) were: BMI = 46 (5%) and 46 (95%); WHR = 46 (5%) and 46 (95%); BF = 1 (5%) and 1 (95%).

In leave-one-out analysis, visual inspection of forest plots showed that no single SNP altered the direction of effect for any metabolite across exposures. For BF, confidence intervals for one or more SNPs crossed the null for every metabolite tested (Representative Figure A.15; all figures GitHub). This was not the case for BMI and WHR, where for many metabolites confidence intervals did not cross the null for any SNPs (Representative Figure A.16; all figures GitHub).

5.3.3 Additional analyses

Additional exposures

Results from additional exposures for BMI showed broadly larger effect estimates but consistent directions of effect across metabolites (Figure 5.10). For the BMI SNPs obtained from a non-UK Biobank GWAS, effect estimates had much wider confidence intervals. Spearman's Rho correlataion of MR results was highest between the two SNP lists from Yengo et al. (2018) (0.98) - correlation between the the Locke et al (2014) SNP list and the COJO SNP list from Yengo et al (2018) (0.9) and the non-COJO SNP list from Yengo et al. (2018) (0.93) were also high.

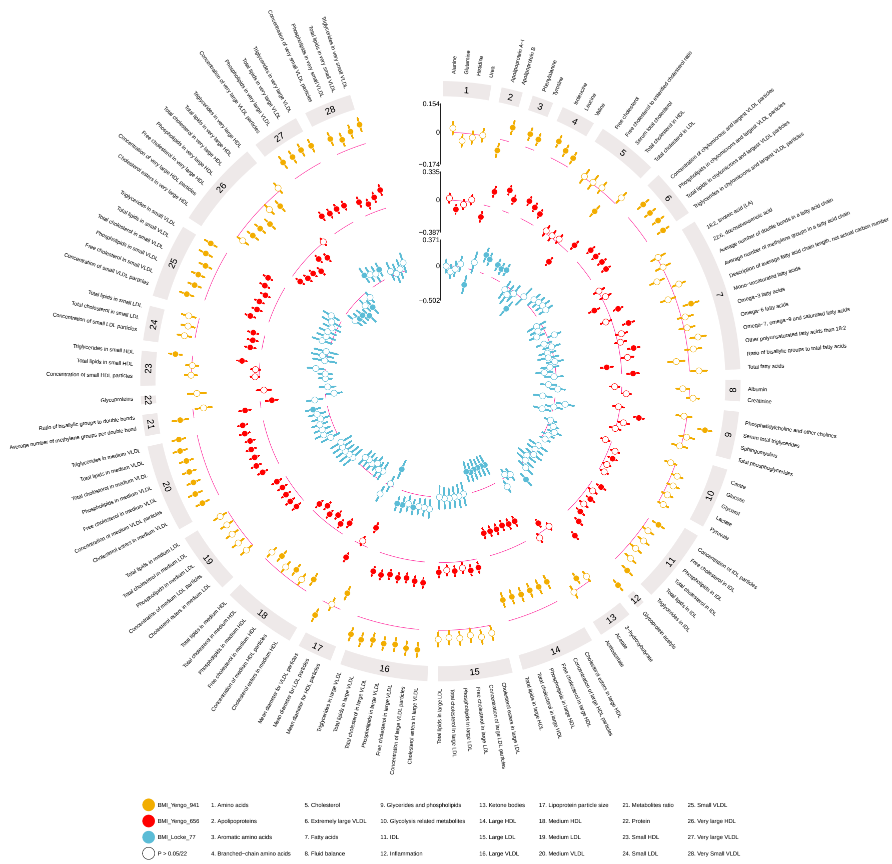

Figure 5.10: Circos plot of IVW-MRE effect estimates for three different BMI SNP lists on 123 NRM derived metabolites

2056 For WHR the global pattern of association was similar between both the main and additional exposure (Figure 5.10) with high correlation between MR results (0.9). Effect estimates were larger for the additional exposure from Shungin et al (2014), for which fewer reuslts reached the multiple testing threshold with wider confidence intervals which crossed the null more often than with the main analysis.

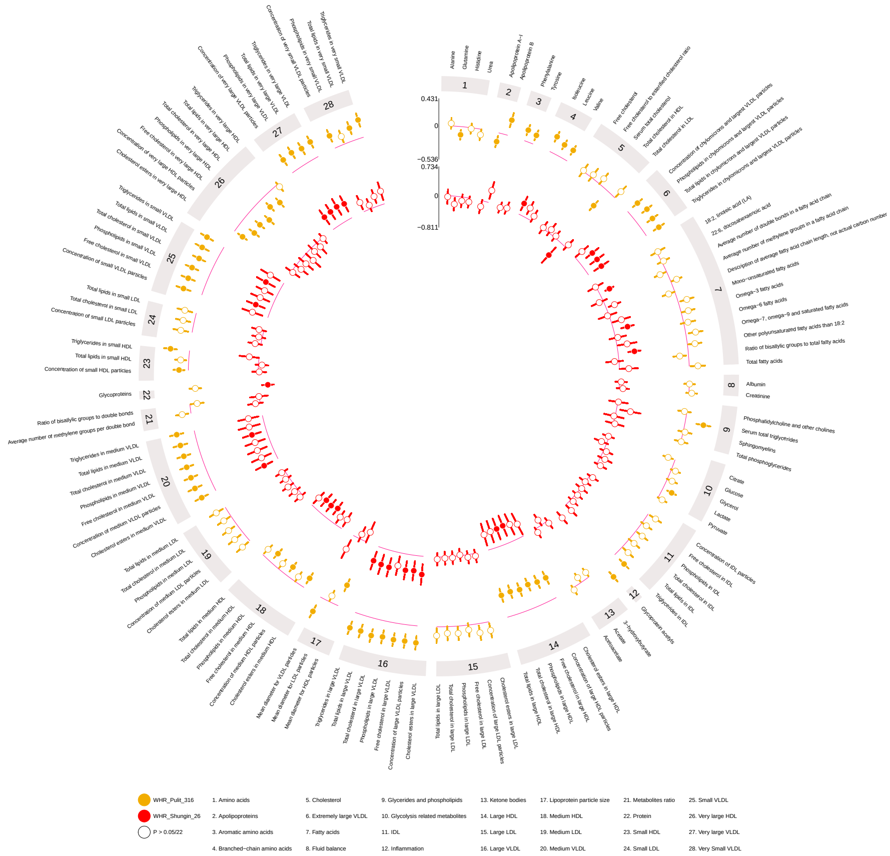

Figure 5.11: Circos plot of IVW-MRE effect estimates for two different WHR SNP lists on 123 NRM derived metabolites

For BF there was considerable similarity between the main analysis and the additional analysis from Lu et al (2016) which did not include two SNPs previousy identified as being associated with favourable adiposity (Figure 5.12). More metabolites reached the multiple testing threshold when using the 5 SNPs from Lu et al (2016) as opposed to the full 7 SNPs, this included associations with

Apolipoprotein A1, Phenylalanine, Tyrosine, Glucose, and Cholesterol esters in very large HDL. For the additional analysis which used 76 SNPs from Hubel et al (2016), MR reuslts were considerbaly smaller and appeared to show conflicting directions of effect with that of the Lu et al. (2016) SNPs (both using 7 and 5 SNPs). Confidence intervals were much tighter and two metabolites (Phenylalanine and Glycoprotein acetyls) reached the multiple testing threshold. Correlation between the two Lu et al (2016) SNP lists was high (0.93), however both the 5 (-0.64) and 7 (-0.52) SNP lists from Lu et al. (2016) showed weaker inverse correaltions with the SNP list from Hubel et al (2016).

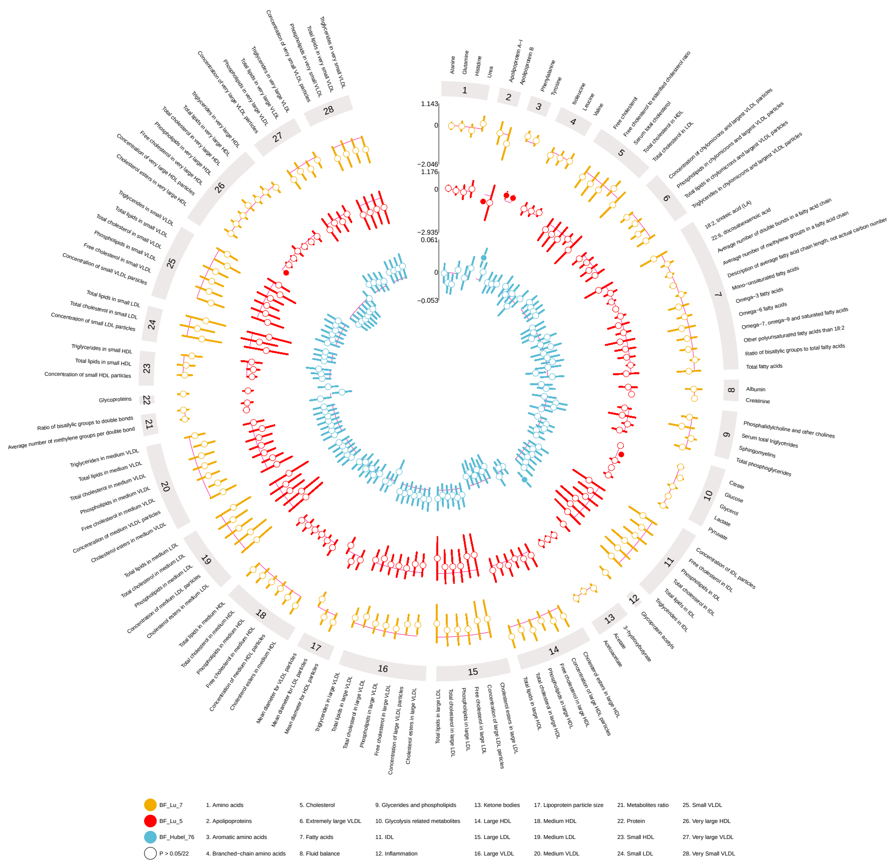

Figure 5.12: Circos plot of IVW-MRE effect estimates for three different BF SNP lists on 123 NRM derived metabolites

Clumped exposures

All SNP lists used as exposures underwent clumping and MR analyses were repeated. Clumping resulted in the removal of the following SNPs due to LD (R^2 >= 0.001) with other variants or absence from the LD reference panel: BMI Locke et al. (2014) = 14, BMI Yengo et al. (2018) using COJO SNPs = 583, BMI Yengo et al. (2018) using non-COJO SNPs = 336, WHR Pulit et al. (2018) = 234, WHR Shungin et al. (2014) = 17, BF Hubel et al. (2018) = 4. No SNPs were removed due to clumping for BF from Lu et al. (2016)[183]. All SNPs, including whether they were removed due to clumping, are presented in the Supplement (Table A.5).

For BMI, correlation between the Yengo COJO (0.9731849), non-COJO (0.9670003), and Locke (0.9782216) non-clumped and clumped MR results was high. Similarly, for WHR MR results from non-clumped and clumped analyses correlation was high for the main exposure (Pulit et al. (2018) = 0.974436) and for the additional exposure (0.9766674). For BF, clumping was not possible for the main exposure, however correlation between the non-clumped and clumped SNP list from Hubel et al. (2018) was high (0.9808851).

5.3.4 Comparison with observational estimates from Chapter 4

In total, 111 metabolites were measured across the observational analysis in adults (conducted in Chapter 4) and the main MR analysis conducted here. Of these, a majority of metabolites showed consistent directions of effect when comparing within exposures between MR and observational results for BMI (n = 107; Spearmans correlation between MR and observational results = 0.56) and WHR (n = 108; Spearmans correlation between MR and observational results = 0.55;Figure 5.13). For BF, a majority (n = 93; Spearmans correaltion between MR and observational results = -0.69) of metabolite results showed opposite directions of effect, e.g. a positive direction of effect may be observed for an MR result but a negative direction of effect for the same metabolite may be observed for the observational analysis.

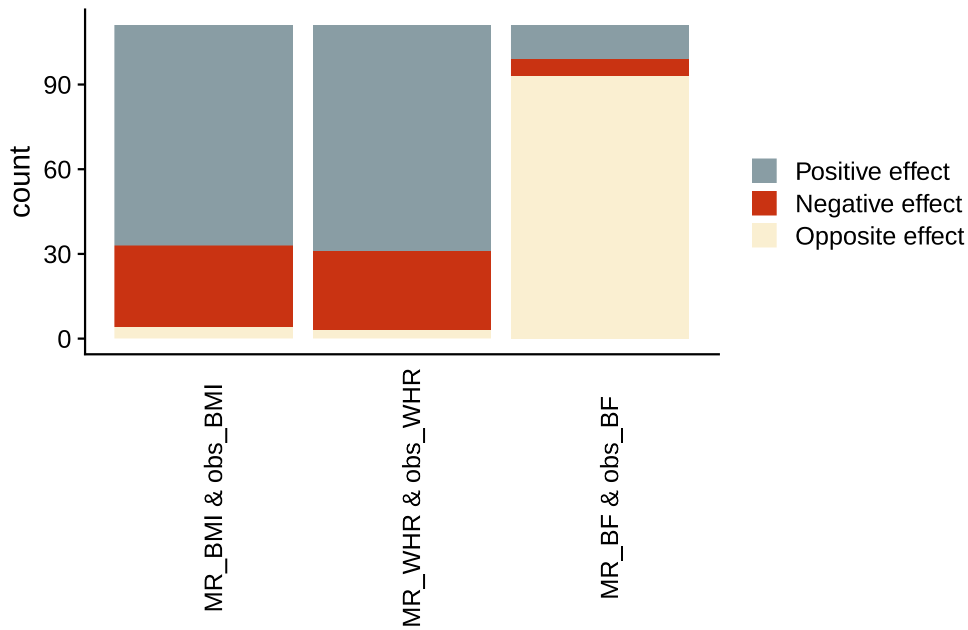

Figure 5.13: Directional consistency across exposures

Figure 5.13 shows the directional consistency between the MR and aboservational analyses for BMI, WHR, and BF exposures. A positive effect reflects the effect estimate from two exposures being in the positive direction; a negative effect reflects betas being in a negative direction; opposite effect reflects different directions for the effect estimates. BMI = body mass index; WHR = waist hip ratio; BF = body fat percentage.

Across the 111 metabolites, a total of 62 reached the multiple testing threshold for BMI in both observational (observational only = 101) and MR (MR only = 62) analyses. This was similar for WHR, where 63 metabolites reached a multiple testing threshold across both observational (observational only = 102) and MR (MR only = 63) analyses. For BF there were 0 metabolites that reached the multiple testing threshold across both MR and observational analyses. This was a result of 0 metabolites reaching the multiple testing threshold in the MR analysis - for the observational analysis a simialr number of metabolites reached the multiple testing threshold (100) as with the BMI and WHR observational analyses.

Of the 62 metabolites that reached the multiple testing threshold for BMI, a total of 62 were directionally consistent across both MR and observational analyses; 45 tests showed a positive direction of effect and 17 showed a negative direction of effect. For WHR, of the 63 metabolites reaching the multiple testing threshold across MR and observational analyses, a total of 63 metabolites were directionally consistent; 45 showed a positive direction of effect and 64 showed a negative direction of effect. When looking at both MR and observational results across BMI and WHR there are a total of 67 metabolites which reach a multiple testing threshold, of these 4 are unique to BMI and 5 are unique to WHR. Combined, there were 58 metabolites which reached the multiple testing threshold across BMI and WHR for MR and observational analsyes. Of these 58, a total of 58 metabolites were directionally consistent across BMI and WHR; 42 showed a positive direction of effect and 16 showed a negative direction of effect.

Across observational and MR analyses for BMI and WHR, 58 results were directionally consistent and met a multiple testing threshold. When looking at these metabolites across all three exposures for MR and observational analyses (Figure 5.14): MR results have wider confidence intervals than observational results, WHR in MR analysis shows broadly larger effects across a majority of metabolites, effect size for BMI in MR analysis is broadly consistent with the three exposures in observational analyses, confidence intervals for BF in MR analysis spans most of the effect estimates for the MR and observational results across a majority of metabolites.

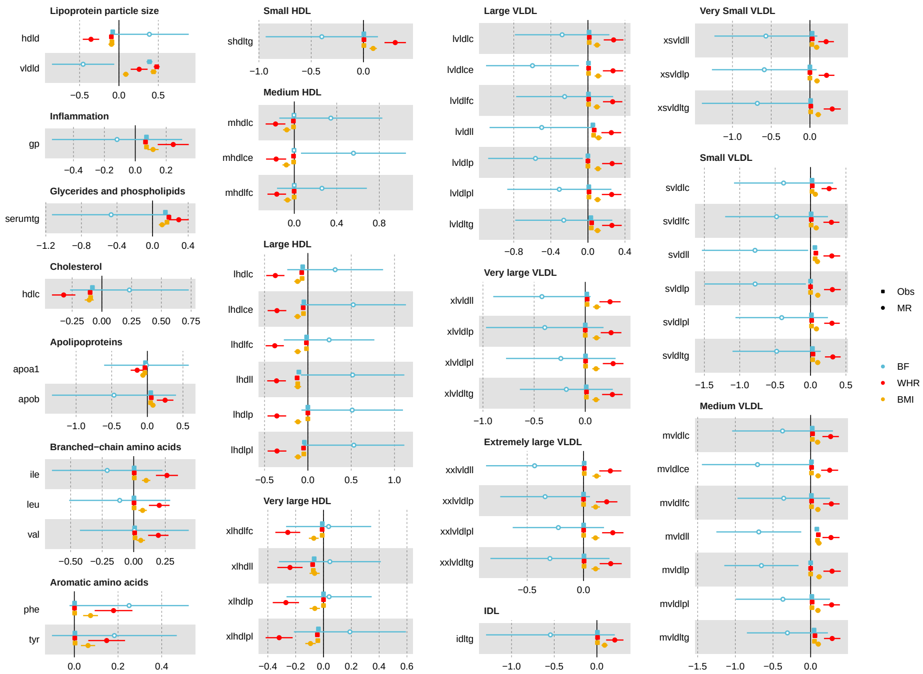

Figure 5.14: Directional consistency across exposures

Figure 5.14 shows the directional consistency between the MR and aboservational analyses for BMI, WHR, and BF exposures. A positive effect reflects the effect estimate from two exposures being in the positive direction; a negative effect reflects betas being in a negative direction; opposite effect reflects different directions for the effect estimates. BMI = body mass index; WHR = waist hip ratio; BF = body fat percentage.

Comparison with Wurtz et al. (2014)[149]

Of the 58 metabolites that were directionally consistent across BMI and WHR and met a multiple testing threshold, for both MR and observational analyses, 11 were also analysed previously by Wurtz et al. (2014)[149]. Comparison of effect estimates across all exposures from MR and observational analysis with results from Wurtz et al. (2014) is presented in Figure 5.15. Observational results (described in 4.3.2) were comparable with observational results from Wurtz et al. (2014) in their direction of effect, and broadly comparable in effect size with overlapping confidence intervals. For the 11 results here however the *Amino acids* subclasses metabolites showed large differences in effect size in both observational and MR analysis compared with Wurtz et al. (2014). Effect sizes were much more similar for the metabolites in the remaining subcalsses (*Lipoprotein particle size*, *Inflammation*, *Cholesterol* and *Apolipoproteins*), however MR results from analysis conducted here was broadly larger.

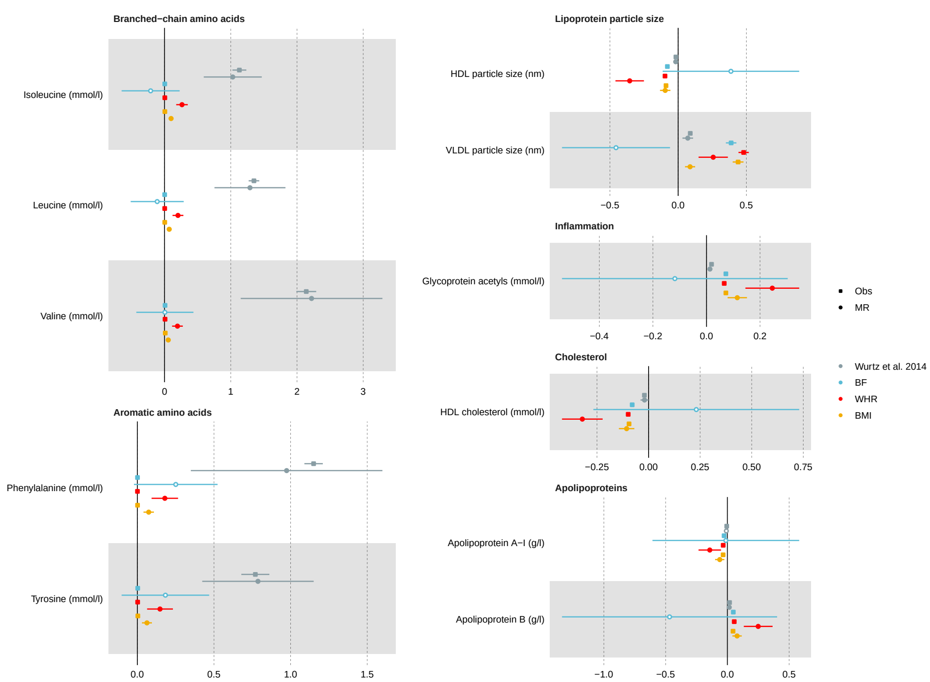

Figure 5.15: Comparison of MR and observational results with observational and MR results from Wurtz et al. (2014)

5.4 Discussion

In this chapter, the influence of increased adiposity on the metabolic profile is demonstrated in an MR framework. The use of MR allowed for the interrogation of causality between BMI, WHR, and BF with the metabolic profile, while accounting for limitations in observational analyses (discussed in Chapter 1 and 4).

Results for BMI and WHR provide evidence for a global association; both show positive and negative effects on whole subclasses of metabolites. On the whole, WHR showed a larger effect across the metabolic profile, however confidence intervals for WHR and BMI mostly overlapped with one another. Evidence for an association between BF and the metabolic profile was lacking; on the whole, directions of effect conflicted with those of BMI and WHR, while effect estimates were larger and confidence intervals much wider.

Sensitivity analysis was broadly consistent with the main analysis across BMI and WHR; *Valine* was the only metabolite that was directionally consistent in sensitivity analysis across BMI and WHR and which reached a multiple testing threshold in the main analysis. There was considerable heterogeneity in the genetic instruments used in the main analysis and in single SNP MR analysis a number of SNPs showed disproportionately larger effect estimates across many metabolites; leave-one-out analysis did not highlight any individual SNP as driving the effect for any metabolite.

Additional analysis aimed to assess whether instruments for BMI and WHR were appropriate given present structural problems in UK Biobank[89] for which instruments were obtained, and whether BF instruments obtained from a GWAS using a mixture of measurment techniques were appropriate. In addition, though studies often report SNPs as being *independent*, whether they are in an MR context was tested by clumping all instrument lists and repeating analyses. Use of additional BMI and WHR exposures showed consistent results with the main analysis, though the widening of confidence intervals obsevred for the non-UK Biobank SNP lists would suggest a considerable increase in power is present when using the larger SNP lists. Considerable difference was observed for BF, where the additional SNP list obtained from UK Biobank resulted in very small effect estimates which on the whole were inverse to the main BF analysis; removal of 2 SNPs from the main BF SNP list resulted in tighter confidence intervals and a number of metabolites reaching the multiple testing threshold – these metabolites showed evidence of association for BMI and WHR in the main analysis. Clumping of SNP lists resulted in large numbers of SNPs being removed from the main BMI and WHR analyses, however results from all clumped and non-clumped SNP lists were highly correlated.

Taken together, results from the main, sensitivity, and additional analyses provide evidence for association between BMI and WHR and metabolites across a majority of subclassed. Though the main analysis for BF showed inconclusive evidence for association, additional analysis highlighted a number of metabolites that were found to be associated with BMI and WHR.

In Chapter 4 observational analysis of BMI, WHR, and BF highlighted association with the global metabolic profile that persisted across time and when adjusted for confounders. Of 111 metabolites measured across observational and MR analyses, all most all showed consistent directions of effect for BMI and WHR. Results for BF however, showed a majority of MR results to be in the opposite direction to observational results. Though correlation between MR and observational results was not very high, when taking into account directional consistency and the multiple testing threshold across MR and observational analysis between BMI and WHR just under half of the metabolites met this criteria. Previous work by Wurtz et al. (2014)[149], discussed in relation to the observational analysis in Chapter 4, highlighted causal associations between adolescent BMI and nuermous metabolites. In comparing results that met the above threshold with those of Wurtz et al. (2014) there is considerable difference in effect size across the board, this is particularly evident for metabolites in the *Amino acids* subclasses.

5.4.1 Limitations

Metabolomics

As discussed in the limitations section of Chapter 4, there is no standardised approach, nor a gold standard, for performing metabolomics quality control. In Chapter 4, quality control, including outlier detection and removal, was performed using the `MetaboQC R` package. Metabolite data here however was obtained from previously reported GWAS's, in which studies used different collection and storage methods. Metabolomics analysis was consistent across all studies and adjustment prior to GWA analysis was made for age, sex, time from last meal if applicable, and the first ten genomic principal components. These adjustments were not all made in the observational analysis. In addition, no description of metabolomic data quality control prior to GWA analysis was provided and so compariosn with that applied in Chapter 4 is difficult.

Exposures

Given that MR relies on the use of an instrument to model the effect of an exposure on an outcome, that instrument needs to be robust and applicable to the exposure. The strength of an exposure is usually measured via an F statistic, for which an arbitrary threshold of > 10 denotes a strong instrument. All of the instruments used here exceeded this threshold. In addition, the variance explained in an exposure by a GWAS can indicate the power afforded in the MR analysis; the variance explained for exposures used in the main analysis varied from ~22% for WHR, to 6% for BMI and ~0.4% for BF. The considerably lower variance explained for BF may have impacted on results, as when instruments which explained less variance for BMI and WHR were used confidence intervals became wider.

The consistent directions of effect observed across BMI and WHR measures adds weight to their associations with metabolites. For BF, conflicting directions of effect were observed when comparing to BMI and WHR. However, confidence intervals were wider and, although they spanned the null in all cases, included the estimates and confidence intervals for BMI and WHR in a majority of cases. There was considerable difference in the sample sizes used in the GWASs for BMI, WHR, and BF. In addition, whereas BMI and WHR were measured in only one way for their respective GWASs, the BF GWAS included measures of BF from DXA and impedance devices. Though, as shown in Chapter 4, DXA and impedance measures of BF are highly correlated, the additional analysis for BF which used only impedance measures in the GWAS showed much greater directional consistency with BMI and WHR and also included a number of metabolites which reached the multiple testing threshold. As BMI, WHR, amd BF observational results are highly directionally consistent, BF results from the main analysis should be looked at in conjunction with those results from the additional analysis as their conflicting directions of effect with BMI and WHR in MR analysis is seemingly inconsistent with previous work and what is perhaps biologically sound. (I DONT LIKE THIS LAST bit 'biologically sound' - re-word, you're trying to say that you would expect BF results to be in the same direction as BMI and WHR as they measure simialr things and all three correlate highly, and observational estimates are all consistent)

Statistical analysis

MR analyses are subject to a number of assumption the main three being: (i) the instrumental variable (Z) is robustly associated with the exposure (X), (ii) there is no independent association of the instrumental variable with the outcome (Y) other than through the exposure, (iii) the instrumental variable is independent of measured or un-measured confounders (U). In this work instruments were obtained from large well-powered GWAS and the F statistic for each instrument was above a nominal threshold. In regards the other two assumptions, formal testing is not possible, however, sensitivity analysis can provide an indication of pleiotropy while results from observational analyses indicates the effects of likely confounders is minimal. Sensitivity analysis, although not comprehensive, was concordant with the main analysis.

The effects of population structure are becoming more apparent in large GWASs[86,87] and this poses an issue for MR studies which use their data. Analyses involving genetic instruments obtained from UK Biobank were repeated using instruments obtained from smaller studies that did not include UK Biobank and results were similar. This goes someway in addressing issues with the studies in which instruments were obtained, however it is still possible that these smaller studies may also have sturctural issues e.g. BMI from Locke et al. (2014)[99].

5.4.2 Summary

There is clear evidence of a causal association between increased adiptosity and the global metabolic profile. This evidence is strengthened for the handful of metabolites that were comparable across MR, observational, and the work conducted by Wurtz et al. (2014), suggesting robust associations with increased adiposity. Some of these metabolites may be involved in the development of adiposity associated diseases, however their roles may also be as markers of increased adiposity or other co-occuring incidents that may be the ultimate intermediates on the pathway to disease development. It is important that when examining assocaitions between metabolites and disease the interrelated nature of metabolites, and the likelihood that they are merely markers of physiological change is taken into account both when performing analyses and examaning results.

Chapter 6

Data visualisation

EpiViz: a tool to visualise large metabolomic association analyses

In Chapters 4 and 5 we observed large metabolic shifts as a result of increased adiposity. These results were presented using Circos plots. Production of the first stage of these plots was inefficient. This chapter details the development and implementation of a web application and `R` package that efficiently creates Circos plots that can be used by the community for similar analyses. The `R` package was used to re-make the plots presented in Chapters 4 and 5 and make those in subsequent chapters.

6.1 Introduction

The metabolome (briefly discussed in Section 1.7) is a complex biological system comprised of the bodies entire small molecules. These small molecules, metabolites, take many forms and act in a multitude of pathways[115]. Metabolites are expressed differentially among cell types and carry information from genetic and non-genetic factors[118,119]. They are the ultimate end-point of a biological process and are therefore seen as the link between genotype and phenotype[115–118].

There are potentially many thousands of metabolites[115] across different cell types, with expression associated with traits and diseases[119,131–135]. However, assigning individual metabolite changes to diseases is difficult[116,117,120] because of the complexity of their interrelationships. The metabolome is made up of many feedback and feed-forward loops, meaning metabolic products of one pathway will likely influence those of another. The intercorrelated nature of metabolites[138] is further complicated by the wide degree of genetic correlation[127] and shared genetic architecture[124–127]. Gaining global overview of association analyses will likely aid interpretation of results. Global overview is of particular importance in MR studies where robust selection of instrumental variables is required to meet methodological assumptions[80].

Forest plots are widely used in metabolomic association analyses[192–197] to visualise and interpret results. They can be easily made, with a number of `R` packages, such as `ggforestplot` and `TwoSampleMR`[177], available. However, when presenting more than 50 data points forest plots are cumbersome and many separate plots are needed. This makes gaining global overview difficult.

An alternative approach is to compress information into a circular rather than vertical/horizontal form (see Figures 3 and 2 from[124] and[125] respectively). Circos plots[198], as implemented in many genetics studies, condense large amounts of information into informative visualisations (see Figure 1A from[199]). However, Circos software is designed for genomic data and written in programming languages unfamiliar to many epidemiologists. The `R` package `circlize`[200] provides most of the functionality of the Circos software but is designed for genomic information and requires an advanced understanding of `R`. Here I present `EpiViz`, a web application and `R` package, that builds on the `circlize`[200] and `ComplexHeatmap`[201] `R` packages. `EpiViz` enables epidemiologists with little programming experience to efficiently create Circos plots with hundreds of variables and gain global overview.

6.2 Methods

6.2.1 Circos plots for association analyses

`EpiViz` adapts and builds on the `Circlize` foundation to create Circos plots compatible with association analysis data. Circos plots are composed of six elements: template, plotting space, tracks, sections, data, legend (Figure 6.1). The template element is a square of defined proportions within which information is plotted. Each additional element is layered onto the template one after the other. The plotting space element is an empty circle which is layered and centred on top of the template. Data is plotted on to the plotting space. An optional extra of the Circos plot, the legend element takes the dimensions of the template and creates a separate plotting space that can be layered on to the bottom of the template element.

The plotting space is separated into tracks and sections. Tracks are laid down as rings within the plotting space. Each track represents a single element of information such as an exposure. Tracks are numbered from the outside to the centre of the circle and coloured separately. Sections divide the plotting space into distinct areas, much like a pie chart. Sections are defined by the data and usually represent groups of outcomes such as metabolite classes. A section track is laid at the outside of the tracks to give a header for each section. The header is referenced in the legend element.

Once the template, plotting space, tracks and sections are laid down, coordinates for each section and track location can be called to plot the data element. Each track and section coordinate, e.g. track 2 section 3, is treated as an individual plotting space. As such, data can be plotted based on the following coordinates: track, section, X, Y. The X axis of each track is defined by the number of rows in the data frame, i.e a data frame with 100 rows will have an X axis of length 100 with each row given an X axis coordinate from 1:100. The Y axis is defined by the minimum and maximum of the data for that track. As such, each track and section coordinate, e.g. track 2 section 3, can be considered an individual plot with a Y axis that is shared by all of the sections in that track. For each position on the X axis the label element of each row is plotted outside of the section header.

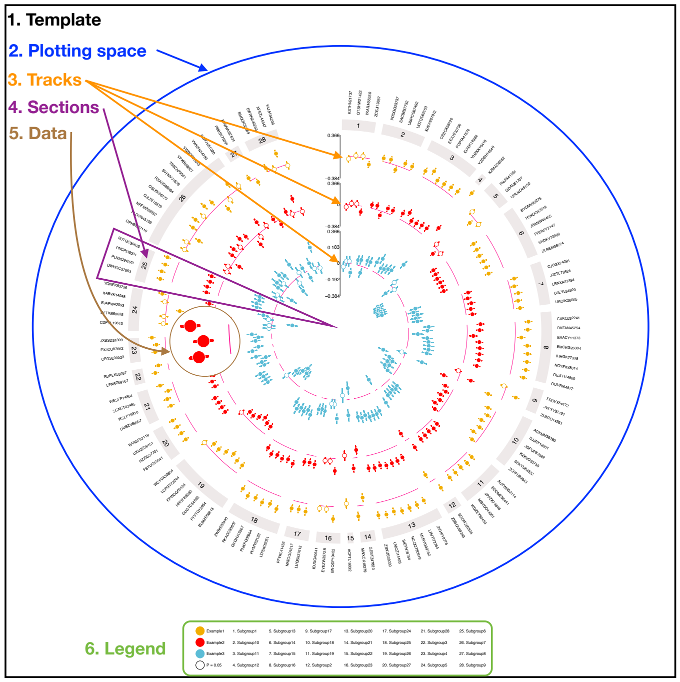

Figure 6.1: Annotated Circos plot highlighting elements of the Circos plot

6.2.2 Implementation

`EpiViz` is a `Shiny` web application and `R` package. `R` (version 3.6.2)[146] and `Shiny`[202] (version 1.4.0) were used to develop the web application and `R` (version 3.6.2) was used to develop the `R` package. `Shiny` is an `R` package that enables development and deployment of web applications written in the `R` programming language. Development of `EpiViz` was progressive and feedback from colleagues (see Section 6.4) was vital in this process.

6.2.3 Operation

The web application is publicly accessible – http://mrcieu.mrsoftware.org/EpiViz/ – and held under an MIT license. Docker was used to containerise the application. The Medical Research Council Integrative Epidemiology Unit at the University of Bristol Shiny server hosts the web application. The web application has been tested on computers running macOS (version 10.14) and Windows (version 10) using: Internet Explorer (version 11; Windows), Google Chrome (version 79; macOS and Windows), Safari (version 13; macOS).

The R package is publicly accessible through GitHub – https://github.com/mattlee821/EpiViz/tree/master/R_package – and held under anMIT license. The R package is accessible on all computers with R version 3.3.0 or higher and has been tested on macOS (version 10.14) and Windows (version 10) running R version 3.3.0 or higher.

A legend function is available for both the web application and R package and is implemented using functions from the ComplexHeatmap[201] R package. By default the colours used for the Circos plot in both the web-application and R package are accessible colours identified using i want hue. Example data is provided on the web application *Home* tab and with the R package using the function EpiViz::EpiViz_data*() where * is 1-3. Example data can be produced for use with the web-application and R package using code on GitHub.

`Shiny` web application

In order to use the web application a web-browser and an internet connection of at least 1Mbps is required. No other system requirements are needed. Upon opening the web application, users are shown a number of example Circos plots created with the application and are directed towards the *Home* tab. The *Home* tab (Figure 6.2) provides users with a short summary of the application, link to the `R` package, and example data for use with the app.

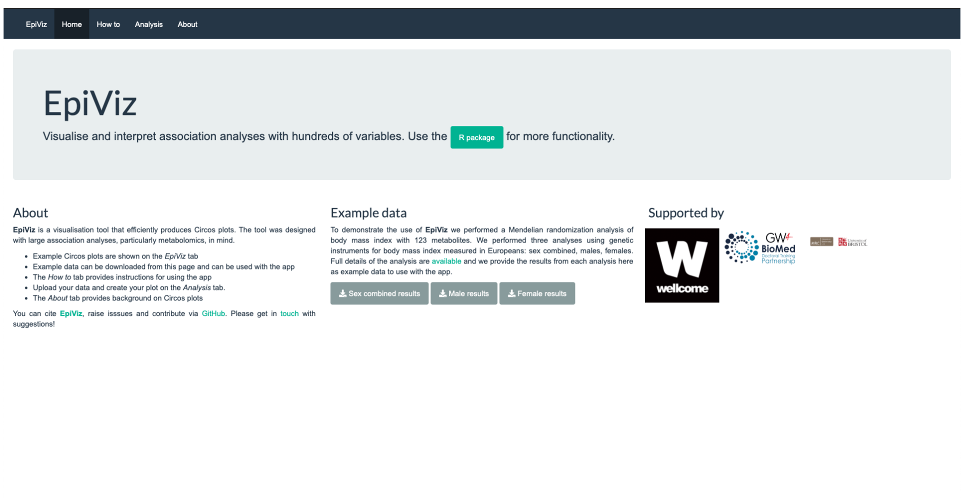

Figure 6.2: Screenshot of the EpiViz web application Home page

The *How to* provides instructions for using the application and is split into three: Step 1 deals with the preparation of data to be used with the application, step 2 deals with how to use the application, and step 3 provides information on potential next steps. Users are instructed to upload one data frame per track of the Circos plot. Each data frame should be a tab delimited text file and `R` code is provided for users to achieve this. The user is guided through an example utilising the example data provided with the application and downloadable on the *Home* tab.

Having prepared their data as instructed in Step 1, users select the *Analysis* tab and upload one data frame for each track of the Circos plot. If formatted as described in the *How to* tab, descriptive information including a volcano plot will be produced automatically (Figure 6.3).

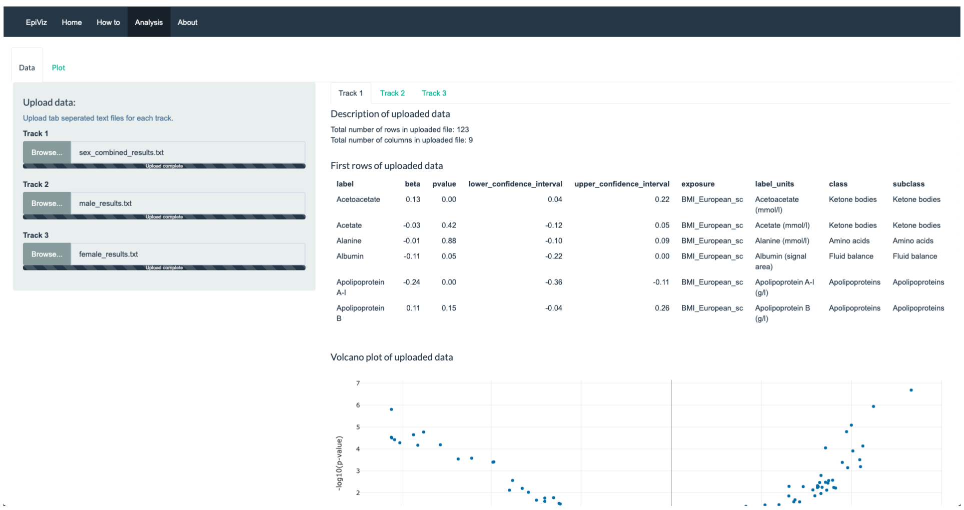

Figure 6.3: Screenshot of the EpiViz web application Analysis page, showing Step 1

If the data frame appears as expected to the user the Circos plot can then be produced by selecting the *Plot* tab. A series of drop down lists are presented which auto-populate with the column names from the first uploaded data frame. The following column information is required for the Circos plot: label, group, estimate, p-value, lower confidence interval, upper confidence interval (Figure 6.4). Users can select one, two, or three tracks for their Circos plot, with data for the respective track coming from the upload data section.

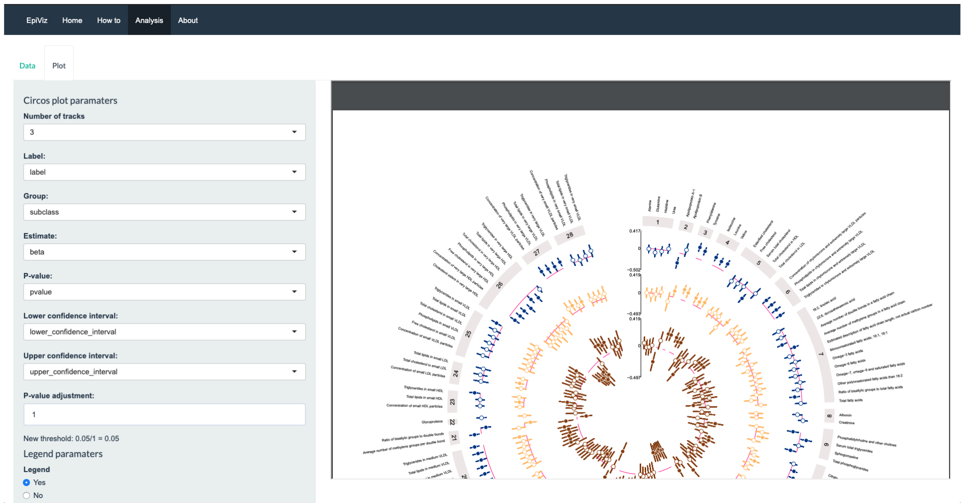

Figure 6.4: Screenshot of the EpiViz web application Analysis page, showing Step 2

A p-value threshold (default 0.05) can be provided to indicate a significance threshold. On the Circos plot a solid point is indicated as reaching the significance threshold and an open point indicates not reaching the threshold. An optional legend function is provided and users can choose the labels for the legend points. The legend is auto-populated using the levels in the `group` column of the up-loaded data frame. Finally, users can select to use *Accessible colours* (default) or *Not accessible colours* for the colours of the points on the Circos plot.

`R` package

The `EpiViz` `R` package is accessed using `R` version 3.3.0 or above. Documentation for using the package to create Circos plots is available as a README on GitHub and includes use cases and troubleshooting. The `R` package can be installed directly from GitHub into R with the following R code:

```r
# Install devtools
install.packages("devtools")
library(devtools)

# Install directly from GitHub
devtools::install_github("mattlee821/EpiViz/R_package")
library(EpiViz)
```

Once installed, users can use the example data provided with the package to produce Figure 6.5, which illustrates the three different types of track available (point, line, bar), using the following R code:

```r
circos_plot(track_number = 3,
            track1_data = EpiViz::EpiViz_data1,
            track2_data = EpiViz::EpiViz_data2,
            track3_data = EpiViz::EpiViz_data3,
            track1_type = "points",
            track2_type = "lines",
            track3_type = "bar",
            label_column = 1,
            section_column = 9,
            estimate_column = 2,
            pvalue_column = 3,
            pvalue_adjustment = 1,
            lower_ci = 4,
```

```
              upper_ci = 5,
              lines_column = 2,
              lines_type = "o",
              bar_column = 2)
```

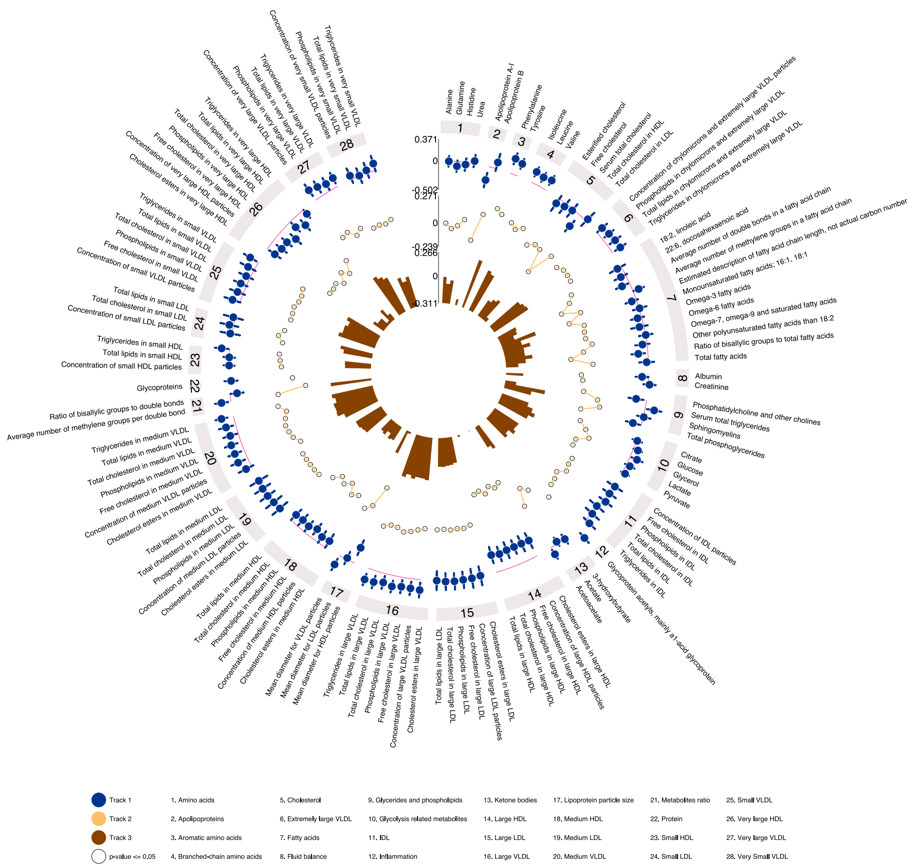

Figure 6.5: Circos plot prduced using EpiViz R package and example data

These Circos plots are designed to be viewed on a screen rather than on paper.

As such the plots are created at a larger scale compared to traditional plots made in R. This means that when viewing the Circos plot in an viewer such as the R Studio Viewer pane the plot appears squashed. Viewers like this should be used only as a guide when making the plot. Instead, plots should saved as PDF using the below code – PDF files can be converted to other image formats.

```
pdf("my_circos_plot.pdf",
    width = 30, height = 30, pointsize = 35)
circos_plot(...
            circle_size = 25)
dev.off()
```

R sets default height, width and pointsize parameters and users should iterate the sizing of the plot adjusting the `width` and `height` functions to get the desired plot size. They should then adjust the `pointsize` function to increase and decrease the size of all information in the plot (labels, points, lines etc.). The numbers provided work with most plots and were used for all examples. In addition, users can adjust the size of the Circos plot directly using the argument `circle_size`. The default for `circle_size` is 25 and smaller numbers increase the size of the circle and larger numbers decrease the size. Finally, users can adjust the height of tracks individually using `track*_height` where $\star$ refers to the track number (see below code). The default for each track is 20 percent of the total size of the circle (the section track is fixed at 5 percent).

```
circos_plot(...
            track1_height = 0.2,
            track2_height = 0.2,
```

```
              track3_height = 0.2)
```

In order to minimise the time required to maintain the `R` package further customisation is achieved by the users themselves. The function is written to aid this customisation with *Default parameters* and *Customisable parameters* located at the top of the `circos_plot()` function script. Guidance and code is provided on GitHub to aid user customisation, for example changing track colours requires users navigating to the *Customisable parameters* section and then to the *Colours* section and replacing the following lines with their desired colours:

```
discrete_palette <- c("#00378f", # track 1 colour
                      "#ffc067", # track 2 colour
                      "#894300") # track 3 colour
```

6.3 Discussion

Circos plots have been used to visualise and provide overview of large association analyses both in the literature[124,125] and this thesis (see Chapters 4, 5 and 9). This has been time consuming and cumbersome. Requiring bespoke code these plots have been challenging to work with when using multiple data sets (see GitHub for example bespoke code).

`EpiViz` provides an efficient way to produce Circos plots for association analyses and can be implemented with little up-front cost. The web application is intended for researchers with limited to no experience of `R`, while those with some experience can gain added functionality from the `R` package. The application of

Circos plots to comparing and gaining global overview of association analyses is presented in Chapters 4, 5 and 9, as well as by colleagues[193].

Though intended to be low maintenance, there is scope for further development of both the web application and R package. Of broad appeal to both is the inclusion of new plotting methods such as the chord diagram which shows relatedness between two nodes. In the case of metabolites a chord diagram would provide greater understanding about the relationship between different sections. In addition, the ability to filter and choose specific sections to display would simplify the plot and highlight potentially meaningful results.

The web application is less flexible than the R package, however there are specific extensions of interest. Firstly interactive plots would provide users the ability to expand sections of interest and display additional information. Rather than a final presentation of the data this would primarily focus on exploration of data. Additionally, introducing features from the R package such as different plot types will broaden the appeal of the web application. These additions are likely to increase the costs of maintenance however.

The R package has extensive scope for enhancement and presents a more efficient investment of time for extensions over the web application due to the flexibility of R. Currently, only a single data point can be plotted on each track at each X axis coordinate. This is to prevent over-crowding. However, if a data set has 50 points for example, adding a second point to each X axis coordinate of the track would not overcrowd the plot.

The current limited customisation afforded with the web application and the R package is designed to reduce the maintenance costs of the author. As a result, functions that users may wish to use, such as multiple point estimates on a single track, must be coded by the user in R. Though guidance is provided on GitHub for such customisations, this additional effort may reduce the utility of the tool, especially among users with little experience of R but very specific requirements. Similarly, although designed to be efficient, users must provide data in a specific format in order to use the web application and R package. R code is provided to aid this effort but the requirement for users with no R experience to create a specific data frame will be off-putting for some.

In order to achieve the desired goal of providing global overview of large association analyses Circos plots must be much larger than traditional plots such as forest plots. As such, Circos plots are best utilised as a tool for the user rather than a reader of a print journal. Circos plots are best viewed using a screen with the ability to zoom in to sections where more detail is required. This fact will reduce the utility of this type of Circos plot in publications as fixed margins will limit the size and resolution of the plot. Resolution can be improved by saving the Circos plots as a PDF file. Many journals do not accept PDF images and will convert these into lossless formats such as PNG or JPEG. This will reduce the resolution provided for readers.

EpiViz is simple and efficient to use. There is potential for EpiViz to become widely used among the community. To pre-empt popularity and provide a stable environment the web application was containerized using Docker and hosted on a server with provision for multiple-users. With popularity it is hoped that a community will help to develop EpiViz further.

6.4 Acknowledgements

`EpiViz` was greatly aided by the `R` packages `Circlize`[200] and `ComplexHeatmap`[201], whose code is freely available and was used as a reference point. The following contributed to the development of `EpiViz`: Luke McGuinness, Osama Mahmoud, Sam Neaves. The following colleagues provided feedback in the development of `EpiViz`: Caroline Bull, Charlie Hatcher, Kurt Taylor, Nancy Mcbride, Neil Goulding, Steph Suddell.

Chapter 7

Clustering metabolites

?????

Chapter 8

Rules for instrumenting clusters

?????

Chapter 9

Mendelian randomization analysis: stage 2

Associations between metabolites and diseases: a Mendelian randomization analysis

Conclusion

Assortative mating https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6221130/#gepi22138-bib-0017

Appendix A

A.1 Chapter 1

A.1.1 Literature search

Manual literature searching is prone to bias. Literature mining tools, though susceptible to publication and other biases, provide an alternative approach enabling a large number of articles to be assessed in a semi-systematic way. MELODI[203], a literature mining tool, was used to identify intermediate diseases between BMI and mortality.

Briefly, MELODI creates individual article sets based on search terms ('body mass index' and 'mortality') and looks for enriched overlapping terms. MELODI uses PubMed and SemMedDB to identify enriched terms. PubMed is a data base of health and biomedical research literature, and SemMedDB is a semantic predications repository built from PubMed citations. Identifying enriched overlapping terms is a two-step process. First, overlapping terms are identified. Second, the degree of overlap given the observed and expected frequency of terms across all articles not just those included in the article sets is quantified.

All articles published from 01/01/2000–09/12/2019 (maximum number of articles per article set is 1,000,000) using the terms 'body mass index' as the source and 'mortality' as the outcome were included. Raw results are available on GitHub. A total of 187,951 and 787,451 articles were retrieved and included in the source and outcome article sets. Using the SemMedDB Triple results a total of 10828 enriched overlapping terms were identified. This included similar terms to 'body mass index' as the source, which were removed (n = 424). A Bonferroni corrected p-value (1.2×10^{-4}) removed 0 terms. Terms were filtered for uniqueness (n =

156) and presence in the following categories: Age Group (n = 152), Bacterium (included because of confounding with pneumonia; n = 4), finding (not an official MELODI category; n = 1), general (not an official MELODI category; n = 1), Fungus (included because of confounding with pneumonia; n = 2), Health Care Activity (n = 5), Human (n = 14), Injury or Poisoning (n = 1), Mammal (animal studies; n = 1), Patient or Disabled Group (n = 8), Population Group (n = 14), Sign or Symptom (n = 1), Virus (included because of confounding; n = 3).

The following terms were removed and merged into immunocompromised host: infections, hospital and opportunistic infections. The following terms were removed because of duplication under different names: cardiac death, sudden death, and sudden cardiac death (merged into cessation of life); coronary arteriosclerosis (atherosclerosis); cardiovascular morbidity, cardiac event, heart diseases, vascular diseases (cardiovascular diseases); depressed mood (depressive disorder); diabetes mellitus and insulin-dependent (diabetic); metabolic diseases (metabolic syndrome). The following terms were removed because they were top-level categories that could either include a wide variety of terms already included or were duplicated by other terms: chronic disease, critical illness, disability, pregnancy complications and perinatal morbidity (included in pregnancy category), pathogenesis. As a result of filtering a total of 77 terms remained. These terms were combined into 9 categories: Cancer, Cardiovascular, immune, Kidney, Liver, Neurological/behavioural, Other, Pregnancy, Respiratory. The 'other' category included traits that did not fit into one of any of the other categories and which did not have aligned traits to form a separate category (Table A.1). The majority of intermediates were cardiovascular related.

It should be noted that the search did not include articles prior to the year

2000 and focussed only on those archived by PubMed. Enrichment aims to reduce the noise introduced when searching hundreds of thousands of articles, however manual curation, which will hold its own biases, is needed in order to obtain an informative list of enriched terms.

Table A.1: Intermediates between body mass index and mortality identified using the literature mining tool MELODI

Intermediate	Category
Primary carcinoma of the liver cells	Cancer
Malignant neoplasm of stomach	Cancer
Malignant neoplasm of prostate	Cancer
Malignant neoplasm of lung	Cancer
Common Neoplasm	Cancer
Liver neoplasms	Cancer
Malignant disease	Cancer
Carcinoma of the Large Intestine	Cancer
Pancreatic carcinoma	Cancer
Heart failure	Cardiovascular
Anemia	Cardiovascular
Dyslipidemias	Cardiovascular
Cerebrovascular accident	Cardiovascular
Cardiovascular Diseases	Cardiovascular
Atherosclerosis	Cardiovascular
Myocardial Infarction	Cardiovascular
Ischemic stroke	Cardiovascular
Acute coronary syndrome	Cardiovascular

Atrial Fibrillation	Cardiovascular
Coronary heart disease	Cardiovascular
Systemic arterial pressure	Cardiovascular
Thrombosis	Cardiovascular
Cerebrovascular Disorders	Cardiovascular
Acute myocardial infarction	Cardiovascular
Sinus rhythm	Cardiovascular
Cardiomyopathies	Cardiovascular
Myocardial Ischemia	Cardiovascular
Peripheral Vascular Diseases	Cardiovascular
Vascular calcification	Cardiovascular
Heart Arrest	Cardiovascular
Myocardial rupture	Cardiovascular
Shock, Cardiogenic	Cardiovascular
Hemorrhage	Cardiovascular
Ischemia	Cardiovascular
Congestive heart failure	Cardiovascular
Ventricular Dysfunction, Left	Cardiovascular
Mitral Valve Insufficiency	Cardiovascular
Hyperglycaemia	Cardiovascular
Pancreatitis	immune
Inflammatory disorder	immune
Immunocompromised Host	immune
Bacteremia	immune
Septicemia	immune

Lupus Erythematosus, Systemic	immune
Sepsis Syndrome	immune
End stage renal failure	Kidney
Kidney Failure, Chronic	Kidney
Glomerular Filtration Rate	Kidney
Kidney Diseases	Kidney
Kidney Failure	Kidney
Renal function	Kidney
Liver diseases	Liver
Non-alcoholic fatty liver	Liver
Liver and Intrahepatic Biliary Tract Carcinoma	Liver
Chronic liver disease	Liver
Depressive disorder	Neurological/behavioural
Dementia	Neurological/behavioural
Metabolic syndrome	Other
Cessation of life	Other
Malnutrition	Other
Diabetic	Other
Multiple Organ Failure	Other
Fibrosis	Other
Deglutition Disorders	Other
Vitamin D Deficiency	Other
Pre-Eclampsia	Pregnancy
Pregnancy	Pregnancy
Hypertension induced by pregnancy	Pregnancy

Tuberculosis	Respiratory
Sleep Apnea, Obstructive	Respiratory
Pneumonia	Respiratory
Chronic Obstructive Airway Disease	Respiratory
Respiration Disorders	Respiratory
Respiratory Distress Syndrome, Adult	Respiratory
Respiratory Tract Infections	Respiratory
Respiratory Failure	Respiratory
Acute respiratory failure	Respiratory

A.2 Chapter 2

A.3 Chapter 3

A.4 Chapter 4

A.4.1 Metabolites

Table A.2: Metabolites available after quality control across all age groups

Metabolite	Label	Class	Subclass	Derived
xsvldlcepct	Cholesterol esters in very small VLDL to total lipids in very small VLDL ratio (%)			
xsvldlcpct	Total cholesterol in very small VLDL to total lipids in very small VLDL ratio (%)			
xsvldlfcpct	Free cholesterol in very small VLDL to total lipids in very small VLDL ratio (%)			

Very Small VLDL ratios

xsvldlplpct	Phospholipids in very small VLDL to total lipids in very small VLDL ratio (%)
xsvldltgpct	Triglycerides in very small VLDL to total lipids in very small VLDL ratio (%)
svldlcepct	Cholesterol esters in small VLDL to total lipids in small VLDL ratio (%)
svldlcpct	Total cholesterol in small VLDL to total lipids in small VLDL ratio (%)

svldlfcpct	Free cholesterol in small VLDL to total lipids in small VLDL ratio (%)	Small VLDL ratios
svldlplpct	Phospholipids in small VLDL to total lipids in small VLDL ratio (%)	
svldltgpct	Triglycerides in small VLDL to total lipids in small VLDL ratio (%)	
mvldlcepct	Cholesterol esters in medium VLDL to total lipids in medium VLDL ratio (%)	

mvldlcpct	Total cholesterol in medium VLDL to total lipids in medium VLDL ratio (%)	Medium VLDL ratios
mvldlfcpct	Free cholesterol in medium VLDL to total lipids in medium VLDL ratio (%)	
mvldlplpct	Phospholipids in medium VLDL to total lipids in medium VLDL ratio (%)	
mvldltgpct	Triglycerides in medium VLDL to total lipids in medium VLDL ratio (%)	

lvldlcepct	Cholesterol esters in large VLDL to total lipids in large VLDL ratio (%)
lvldlcpct	Total cholesterol in large VLDL to total lipids in large VLDL ratio (%)
lvldlfcpct	Free cholesterol in large VLDL to total lipids in large VLDL ratio (%)
lvldlplpct	Phospholipids in large VLDL to total lipids in large VLDL ratio (%)

lvldltgpct	Triglycerides in large VLDL to total lipids in large VLDL ratio (%)
xlvldlcepct	Cholesterol esters in very large VLDL to total lipids in very large VLDL ratio (%)
xlvldlcpct	Total cholesterol in very large VLDL to total lipids in very large VLDL ratio (%)
xlvldlfcpct	Free cholesterol in very large VLDL to total lipids in very large VLDL ratio (%)

xlvldlplpct	Phospholipids in very large VLDL to total lipids in very large VLDL ratio (%)	Very large VLDL ratios
xlvldltgpct	Triglycerides in very large VLDL to total lipids in very large VLDL ratio (%)	
xxlvldlcepct	Cholesterol esters in chylomicrons and extremely large VLDL to total lipids in chylomicrons and extremely large VLDL ratio (%)	

xxlvldlcpct	Total cholesterol in chylomicrons and extremely large VLDL to total lipids in chylomicrons and extremely large VLDL ratio (%)
xxlvldlfcpct	Free cholesterol in chylomicrons and extremely large VLDL to total lipids in chylomicrons and extremely large VLDL ratio (%)

Extremely large VLDL ratios

xxlvldlplpct	Phospholipids in chylomicrons and extremely large VLDL to total lipids in chylomicrons and extremely large VLDL ratio (%)
xxlvldltgpct	Triglycerides in chylomicrons and extremely large VLDL to total lipids in chylomicrons and extremely large VLDL ratio (%)
idlcepct	Cholesterol esters in IDL to total lipids in IDL ratio (%)

idlcpct	Total cholesterol in IDL to total lipids in IDL ratio (%)	IDL ratios
idlfcpct	Free cholesterol in IDL to total lipids in IDL ratio (%)	
idlplpct	Phospholipids in IDL to total lipids in IDL ratio (%)	
idltgpct	Triglycerides in IDL to total lipids in IDL ratio (%)	
sldlcepct	Cholesterol esters in small LDL to total lipids in small LDL ratio (%)	

sldlcpct	Total cholesterol in small LDL to total lipids in small LDL ratio (%)	
sldlfcpct	Free cholesterol in small LDL to total lipids in small LDL ratio (%)	
sldlplpct	Phospholipids in small LDL to total lipids in small LDL ratio (%)	Small LDL ratios
sldltgpct	Triglycerides in small LDL to total lipids in small LDL ratio (%)	

mldlcepct	Cholesterol esters in medium LDL to total lipids in medium LDL ratio (%)
mldlcpct	Total cholesterol in medium LDL to total lipids in medium LDL ratio (%)
mldlfcpct	Free cholesterol in medium LDL to total lipids in medium LDL ratio (%)
mldlplpct	Phospholipids in medium LDL to total lipids in medium LDL ratio (%)

Medium LDL ratios

mldltgpct	Triglycerides in medium LDL to total lipids in medium LDL ratio (%)	
lldlcepct	Cholesterol esters in large LDL to total lipids in large LDL ratio (%)	
lldlcpct	Total cholesterol in large LDL to total lipids in large LDL ratio (%)	
lldlfcpct	Free cholesterol in large LDL to total lipids in large LDL ratio (%)	

		Large LDL ratios
lldlplpct	Phospholipids in large LDL to total lipids in large LDL ratio (%)	
lldltgpct	Triglycerides in large LDL to total lipids in large LDL ratio (%)	
shdlcepct	Cholesterol esters in small HDL to total lipids in small HDL ratio (%)	
shdlcpct	Total cholesterol in small HDL to total lipids in small HDL ratio (%)	

shdlfcpct	Free cholesterol in small HDL to total lipids in small HDL ratio (%)	Small HDL ratios
shdlplpct	Phospholipids in small HDL to total lipids in small HDL ratio (%)	
shdltgpct	Triglycerides in small HDL to total lipids in small HDL ratio (%)	
mhdlcepct	Cholesterol esters in medium HDL to total lipids in medium HDL ratio (%)	

mhdlcpct	Total cholesterol in medium HDL to total lipids in medium HDL ratio (%)	Medium HDL ratios
mhdlfcpct	Free cholesterol in medium HDL to total lipids in medium HDL ratio (%)	
mhdlplpct	Phospholipids in medium HDL to total lipids in medium HDL ratio (%)	
mhdltgpct	Triglycerides in medium HDL to total lipids in medium HDL ratio (%)	

lhdlcepct	Cholesterol esters in large HDL to total lipids in large HDL ratio (%)
lhdlcpct	Total cholesterol in large HDL to total lipids in large HDL ratio (%)
lhdlfcpct	Free cholesterol in large HDL to total lipids in large HDL ratio (%)
lhdlplpct	Phospholipids in large HDL to total lipids in large HDL ratio (%)

lhdltgpct	Triglycerides in large HDL to total lipids in large HDL ratio (%)
xlhdlcepct	Cholesterol esters in very large HDL to total lipids in very large HDL ratio (%)
xlhdlcpct	Total cholesterol in very large HDL to total lipids in very large HDL ratio (%)
xlhdlfcpct	Free cholesterol in very large HDL to total lipids in very large HDL ratio (%)

		Very large HDL ratios
xlhdlplpct	Phospholipids in very large HDL to total lipids in very large HDL ratio (%)	
xlhdltgpct	Triglycerides in very large HDL to total lipids in very large HDL ratio (%)	
xsvldlc	Total cholesterol in very small VLDL (mmol/l)	
xsvldlce	Cholesterol esters in very small VLDL (mmol/l)	
xsvldlfc	Free cholesterol in very small VLDL (mmol/l)	

xsvldll	Total lipids in very small VLDL (mmol/l)	Very Small VLDL
xsvldlp	Concentration of very small VLDL particles (mol/l)	
xsvldlpl	Phospholipids in very small VLDL (mmol/l)	
xsvldltg	Triglycerides in very small VLDL (mmol/l)	
svldlc	Total cholesterol in small VLDL (mmol/l)	

svldlce	Cholesterol esters in small VLDL (mmol/l)	
svldlfc	Free cholesterol in small VLDL (mmol/l)	
svldll	Total lipids in small VLDL (mmol/l)	
svldlp	Concentration of small VLDL particles (mol/l)	Small VLDL
svldlpl	Phospholipids in small VLDL (mmol/l)	
svldltg	Triglycerides in small VLDL (mmol/l)	

mvldlc	Total cholesterol in medium VLDL (mmol/l)
mvldlce	Cholesterol esters in medium VLDL (mmol/l)
mvldlfc	Free cholesterol in medium VLDL (mmol/l)
mvldll	Total lipids in medium VLDL (mmol/l)
mvldlp	Concentration of medium VLDL particles (mol/l)

mvldlpl	Phospholipids in medium VLDL (mmol/l)	Medium VLDL
mvldltg	Triglycerides in medium VLDL (mmol/l)	
lvldlc	Total cholesterol in large VLDL (mmol/l)	
lvldlce	Cholesterol esters in large VLDL (mmol/l)	
lvldlfc	Free cholesterol in large VLDL (mmol/l)	
lvldll	Total lipids in large VLDL (mmol/l)	
lvldlp	Concentration of large VLDL particles (mol/l)	

lvldlpl	Phospholipids in large VLDL (mmol/l)	Large VLDL
lvldltg	Triglycerides in large VLDL (mmol/l)	
xlvldlc	Total cholesterol in very large VLDL (mmol/l)	
xlvldlce	Cholesterol esters in very large VLDL (mmol/l)	
xlvldlfc	Free cholesterol in very large VLDL (mmol/l)	
xlvldll	Total lipids in very large VLDL (mmol/l)	

xlvldlp	Concentration of very large VLDL particles (mol/l)	Very large VLDL
xlvldlpl	Phospholipids in very large VLDL (mmol/l)	
xlvldltg	Triglycerides in very large VLDL (mmol/l)	
xxlvldlc	Total cholesterol in chylomicrons and extremely large VLDL (mmol/l)	
xxlvldlce	Cholesterol esters in chylomicrons and extremely large VLDL (mmol/l)	

xxlvldlfc	Free cholesterol in chylomicrons and extremely large VLDL (mmol/l)
xxlvldll	Total lipids in chylomicrons and extremely large VLDL (mmol/l)
xxlvldlp	Concentration of chylomicrons and extremely large VLDL particles (mol/l)
xxlvldlpl	Phospholipids in chylomicrons and extremely large VLDL (mmol/l)

xxlvldltg	Triglycerides in chylomicrons and extremely large VLDL (mmol/l)
idlc	Total cholesterol in IDL (mmol/l)
idlce	Cholesterol esters in IDL (mmol/l)
idlfc	Free cholesterol in IDL (mmol/l)
idll	Total lipids in IDL (mmol/l)
idlp	Concentration of IDL particles (mol/l)
idlpl	Phospholipids in IDL (mmol/l)

idltg	Triglycerides in IDL (mmol/l)	
sldlc	Total cholesterol in small LDL (mmol/l)	
sldlce	Cholesterol esters in small LDL (mmol/l)	
sldlfc	Free cholesterol in small LDL (mmol/l)	
sldll	Total lipids in small LDL (mmol/l)	
sldlp	Concentration of small LDL particles (mol/l)	Small LDL
sldlpl	Phospholipids in small LDL (mmol/l)	
sldltg	Triglycerides in small LDL (mmol/l)	

mldlc	Total cholesterol in medium LDL (mmol/l)
mldlce	Cholesterol esters in medium LDL (mmol/l)
mldlfc	Free cholesterol in medium LDL (mmol/l)
mldll	Total lipids in medium LDL (mmol/l)
mldlp	Concentration of medium LDL particles (mol/l)

mldlpl	Phospholipids in medium LDL (mmol/l)
mldltg	Triglycerides in medium LDL (mmol/l)
lldlc	Total cholesterol in large LDL (mmol/l)
lldlce	Cholesterol esters in large LDL (mmol/l)
lldlfc	Free cholesterol in large LDL (mmol/l)
lldll	Total lipids in large LDL (mmol/l)
lldlp	Concentration of large LDL particles (mol/l)

lldlpl	Phospholipids in large LDL (mmol/l)	Large LDL
lldltg	Triglycerides in large LDL (mmol/l)	
shdlc	Total cholesterol in small HDL (mmol/l)	
shdlce	Cholesterol esters in small HDL (mmol/l)	
shdlfc	Free cholesterol in small HDL (mmol/l)	
shdll	Total lipids in small HDL (mmol/l)	
shdlp	Concentration of small HDL particles (mol/l)	
shdlpl	Phospholipids in small HDL (mmol/l)	

shdltg	Triglycerides in small HDL (mmol/l)
mhdlc	Total cholesterol in medium HDL (mmol/l)
mhdlce	Cholesterol esters in medium HDL (mmol/l)
mhdlfc	Free cholesterol in medium HDL (mmol/l)
mhdll	Total lipids in medium HDL (mmol/l)
mhdlp	Concentration of medium HDL particles (mol/l)

mhdlpl	Phospholipids in medium HDL (mmol/l)	Medium HDL
mhdltg	Triglycerides in medium HDL (mmol/l)	
lhdlc	Total cholesterol in large HDL (mmol/l)	
lhdlce	Cholesterol esters in large HDL (mmol/l)	
lhdlfc	Free cholesterol in large HDL (mmol/l)	
lhdll	Total lipids in large HDL (mmol/l)	
lhdlp	Concentration of large HDL particles (mol/l)	

lhdlpl	Phospholipids in large HDL (mmol/l)	Large HDL
lhdltg	Triglycerides in large HDL (mmol/l)	
xlhdlc	Total cholesterol in very large HDL (mmol/l)	
xlhdlce	Cholesterol esters in very large HDL (mmol/l)	
xlhdlfc	Free cholesterol in very large HDL (mmol/l)	
xlhdll	Total lipids in very large HDL (mmol/l)	

xlhdlp	Concentration of very large HDL particles (mol/l)		Very large HDL
xlhdlpl	Phospholipids in very large HDL (mmol/l)		
xlhdltg	Triglycerides in very large HDL (mmol/l)		
hdld	Mean diameter for HDL particles (nm)	Lipoprotein particle size	Lipoprotein particle size
ldld	Mean diameter for LDL particles (nm)		
vldld	Mean diameter for VLDL particles (nm)		
acace	Acetoacetate (mmol/l)		
ace	Acetate (mmol/l)		

		Ketone bodies	Ketone bodies
bohbut	3-hydroxybutyrate (mmol/l)		
gp	Glycoprotein acetyls, mainly a1-acid glycoprotein (mmol/l)	Inflammation	Inflammation
cit	Citrate (mmol/l)		
glc	Glucose (mmol/l)		
lac	Lactate (mmol/l)	Glycolysis related metabolites	Glycolysis related metabolites
pyr	Pyruvate (mmol/l)		
dag	Diacylglycerol (mmol/l)		
hdltg	Triglycerides in HDL (mmol/l)		
ldltg	Triglycerides in LDL (mmol/l)		

pc	Phosphatidylcholine and other cholines (mmol/l)	Glycerides and phospholipids	Glycerides and phospholipids
serumtg	Serum total triglycerides (mmol/l)		
sm	Sphingomyelins (mmol/l)		
totcho	Total cholines (mmol/l)		
totpg	Total phosphoglycerides (mmol/l)		
vldltg	Triglycerides in VLDL (mmol/l)		
alb	Albumin (signal area)	Fluid balance	Fluid balance
crea	Creatinine (mmol/l)		

clafa	Ratio of conjugated linoleic acid to total fatty acids (%)
dhafa	Ratio of 22:6 docosahexaenoic acid to total fatty acids (%)
faw3fa	Ratio of omega-3 fatty acids to total fatty acids (%)
faw6fa	Ratio of omega-6 fatty acids to total fatty acids (%)
lafa	Ratio of 18:2 linoleic acid to total fatty acids (%)

mufafa	Ratio of monounsaturated fatty acids to total fatty acids (%)	Fatty acids ratios	Fatty acids ratios	yes
pufafa	Ratio of polyunsaturated fatty acids to total fatty acids (%)			
sfafa	Ratio of saturated fatty acids to total fatty acids (%)			
cla	Conjugated linoleic acid (mmol/l)			
dha	22:6, docosahexaenoic acid (mmol/l)			

falen	Estimated description of fatty acid chain length, not actual carbon number
faw3	Omega-3 fatty acids (mmol/l)
faw6	Omega-6 fatty acids (mmol/l)
la	18:2, linoleic acid (mmol/l)
mufa	Monounsaturated fatty acids; 16:1, 18:1 (mmol/l)
pufa	Polyunsaturated fatty acids (mmol/l)
sfa	Saturated fatty acids (mmol/l)

Fatty acids Fatty acids

totfa	Total fatty acids (mmol/l)
unsat	Estimated degree of unsaturation
estc	Esterified cholesterol (mmol/l)
freec	Free cholesterol (mmol/l)
hdl2c	Total cholesterol in HDL2 (mmol/l)
hdl3c	Total cholesterol in HDL3 (mmol/l)
hdlc	Total cholesterol in HDL (mmol/l)
ldlc	Total cholesterol in LDL (mmol/l)

		Cholesterol	Cholesterol
remnantc	Remnant cholesterol (non-HDL, non-LDL -cholesterol) (mmol/l)		
serumc	Serum total cholesterol (mmol/l)		
vldlc	Total cholesterol in VLDL (mmol/l)		
apoa1	Apolipoprotein A-I (g/l)		
apob	Apolipoprotein B (g/l)	Apolipoproteins	Apolipoproteins
apobapoa1	Ratio of apolipoprotein B to apolipoprotein A-I		
ile	Isoleucine (mmol/l)		
leu	Leucine (mmol/l)		

val	Valine (mmol/l)	Amino acids	Branched-chain amino acids	
phe	Phenylalanine (mmol/l)		Aromatic amino acids	
tyr	Tyrosine (mmol/l)			
ala	Alanine (mmol/l)		Amino acids	
gln	Glutamine (mmol/l)			
his	Histidine (mmol/l)			
dagtg	Ratio of diacylglycerol to triglycerides (%)	Glycerides and phospholipids ratios		yes
tgpg	Ratio of triglycerides to phosphoglycerides ratio (%)			
unsatdeg				

A.4.2 Tables of results

Table A.3: Results of linear regression analysis of measures of increased adiposity and metabolites among different age groups

Metabolite	Subclass	Model	Group	Exposure	Beta	Lower CI	Upper CI	p-value
Isoleucine (mmol/l)	Branched-chain amino acids	model1	children	bmi	0.0032	0.0026	0.0038	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			whr	0.0029	0.0023	0.0035	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			bf	0.0023	0.0017	0.0029	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids		adolescents	bmi	0.0019	0.0014	0.0025	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			bf	0.0016	0.0009	0.0024	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids		young_adults	bmi	0.0039	0.0035	0.0043	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			whr	0.0035	0.0030	0.0040	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			bf	0.0036	0.0031	0.0041	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids		adults	bmi	0.0047	0.0043	0.0051	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			whr	0.0042	0.0038	0.0046	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			bf	0.0036	0.0032	0.0040	0.0000

Isoleucine (mmol/l)	Branched-chain amino acids		children	bmi	0.0034	0.0028	0.0041	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			whr	0.0029	0.0023	0.0035	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			bf	0.0022	0.0016	0.0029	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids		adolescents	bmi	0.0021	0.0015	0.0026	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			bf	0.0017	0.0009	0.0024	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids	model2	young_adults	bmi	0.0039	0.0035	0.0044	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			whr	0.0035	0.0030	0.0040	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			bf	0.0036	0.0031	0.0041	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids		adults	bmi	0.0046	0.0042	0.0050	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			whr	0.0041	0.0037	0.0045	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			bf	0.0035	0.0031	0.0039	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids		adolescents	bmi	0.0012	0.0003	0.0022	0.0138
Isoleucine (mmol/l)	Branched-chain amino acids			bf	0.0011	-0.0002	0.0023	0.0914
Isoleucine (mmol/l)	Branched-chain amino acids			bmi	0.0045	0.0036	0.0055	0.0000

Isoleucine (mmol/l)	Branched-chain amino acids	model3	young_adults	whr	0.0032	0.0023	0.0042	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			bf	0.0039	0.0028	0.0050	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids		adults	bmi	0.0047	0.0043	0.0052	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			whr	0.0042	0.0037	0.0046	0.0000
Isoleucine (mmol/l)	Branched-chain amino acids			bf	0.0036	0.0032	0.0040	0.0000
Leucine (mmol/l)	Branched-chain amino acids		children	bmi	0.0021	0.0016	0.0026	0.0000
Leucine (mmol/l)	Branched-chain amino acids			whr	0.0016	0.0011	0.0022	0.0000
Leucine (mmol/l)	Branched-chain amino acids			bf	0.0013	0.0008	0.0018	0.0000
Leucine (mmol/l)	Branched-chain amino acids		adolescents	bmi	0.0012	0.0008	0.0016	0.0000
Leucine (mmol/l)	Branched-chain amino acids			bf	0.0006	0.0001	0.0012	0.0301
Leucine (mmol/l)	Branched-chain amino acids		young_adults	bmi	0.0039	0.0035	0.0044	0.0000
Leucine (mmol/l)	Branched-chain amino acids			whr	0.0032	0.0027	0.0037	0.0000
Leucine (mmol/l)	Branched-chain amino acids			bf	0.0032	0.0027	0.0037	0.0000
Leucine (mmol/l)	Branched-chain amino acids			bmi	0.0029	0.0026	0.0033	0.0000

Leucine (mmol/l)	Branched-chain amino acids	model1	adults	whr	0.0025	0.0021	0.0028	0.0000
Leucine (mmol/l)	Branched-chain amino acids			bf	0.0019	0.0016	0.0022	0.0000
Leucine (mmol/l)	Branched-chain amino acids	model2	children	bmi	0.0022	0.0016	0.0027	0.0000
Leucine (mmol/l)	Branched-chain amino acids			whr	0.0017	0.0012	0.0022	0.0000
Leucine (mmol/l)	Branched-chain amino acids			bf	0.0011	0.0006	0.0017	0.0000
Leucine (mmol/l)	Branched-chain amino acids		adolescents	bmi	0.0012	0.0007	0.0017	0.0000
Leucine (mmol/l)	Branched-chain amino acids			bf	0.0005	0.0000	0.0011	0.0689
Leucine (mmol/l)	Branched-chain amino acids		young_adults	bmi	0.0041	0.0036	0.0045	0.0000
Leucine (mmol/l)	Branched-chain amino acids			whr	0.0032	0.0027	0.0037	0.0000
Leucine (mmol/l)	Branched-chain amino acids			bf	0.0033	0.0028	0.0039	0.0000
Leucine (mmol/l)	Branched-chain amino acids		adults	bmi	0.0030	0.0027	0.0033	0.0000
Leucine (mmol/l)	Branched-chain amino acids			whr	0.0025	0.0021	0.0028	0.0000
Leucine (mmol/l)	Branched-chain amino acids			bf	0.0020	0.0016	0.0023	0.0000
Leucine (mmol/l)	Branched-chain amino acids			bmi	0.0006	-0.0002	0.0013	0.1554

Leucine (mmol/l)	Branched-chain amino acids	model3	adolescents	bf	0.0002	-0.0008	0.0012	0.7121
Leucine (mmol/l)	Branched-chain amino acids		young_adults	bmi	0.0046	0.0036	0.0056	0.0000
Leucine (mmol/l)	Branched-chain amino acids			whr	0.0031	0.0021	0.0041	0.0000
Leucine (mmol/l)	Branched-chain amino acids			bf	0.0037	0.0025	0.0048	0.0000
Leucine (mmol/l)	Branched-chain amino acids		adults	bmi	0.0032	0.0028	0.0036	0.0000
Leucine (mmol/l)	Branched-chain amino acids			whr	0.0027	0.0023	0.0030	0.0000
Leucine (mmol/l)	Branched-chain amino acids			bf	0.0022	0.0018	0.0025	0.0000
Valine (mmol/l)	Branched-chain amino acids		children	bmi	0.0057	0.0045	0.0068	0.0000
Valine (mmol/l)	Branched-chain amino acids			whr	0.0032	0.0021	0.0044	0.0000
Valine (mmol/l)	Branched-chain amino acids			bf	0.0049	0.0037	0.0060	0.0000
Valine (mmol/l)	Branched-chain amino acids		adolescents	bmi	0.0055	0.0042	0.0069	0.0000
Valine (mmol/l)	Branched-chain amino acids			bf	0.0058	0.0041	0.0075	0.0000
Valine (mmol/l)	Branched-chain amino acids			bmi	0.0086	0.0075	0.0096	0.0000
Valine (mmol/l)	Branched-chain amino acids			whr	0.0052	0.0040	0.0065	0.0000

		model1	young_adults					
Valine (mmol/l)	Branched-chain amino acids			bf	0.0063	0.0051	0.0076	0.0000
Valine (mmol/l)	Branched-chain amino acids		adults	bmi	0.0106	0.0097	0.0116	0.0000
Valine (mmol/l)	Branched-chain amino acids			whr	0.0076	0.0067	0.0086	0.0000
Valine (mmol/l)	Branched-chain amino acids			bf	0.0077	0.0068	0.0086	0.0000
Valine (mmol/l)	Branched-chain amino acids		children	bmi	0.0062	0.0049	0.0075	0.0000
Valine (mmol/l)	Branched-chain amino acids			whr	0.0033	0.0021	0.0045	0.0000
Valine (mmol/l)	Branched-chain amino acids			bf	0.0050	0.0037	0.0063	0.0000
Valine (mmol/l)	Branched-chain amino acids		adolescents	bmi	0.0057	0.0043	0.0071	0.0000
Valine (mmol/l)	Branched-chain amino acids			bf	0.0057	0.0039	0.0075	0.0000
Valine (mmol/l)	Branched-chain amino acids		young_adults	bmi	0.0086	0.0075	0.0097	0.0000
Valine (mmol/l)	Branched-chain amino acids			whr	0.0052	0.0039	0.0064	0.0000
Valine (mmol/l)	Branched-chain amino acids			bf	0.0063	0.0050	0.0075	0.0000
Valine (mmol/l)	Branched-chain amino acids			bmi	0.0106	0.0096	0.0115	0.0000
Valine (mmol/l)	Branched-chain amino acids			whr	0.0075	0.0066	0.0085	0.0000

		model2						
Valine (mmol/l)	Branched-chain amino acids		adults	bf	0.0076	0.0066	0.0086	0.0000
Valine (mmol/l)	Branched-chain amino acids	model3	adolescents	bmi	0.0037	0.0012	0.0062	0.0039
Valine (mmol/l)	Branched-chain amino acids			bf	0.0038	0.0006	0.0070	0.0218
Valine (mmol/l)	Branched-chain amino acids		young_adults	bmi	0.0096	0.0072	0.0120	0.0000
Valine (mmol/l)	Branched-chain amino acids			whr	0.0050	0.0025	0.0075	0.0001
Valine (mmol/l)	Branched-chain amino acids			bf	0.0078	0.0050	0.0105	0.0000
Valine (mmol/l)	Branched-chain amino acids		adults	bmi	0.0110	0.0099	0.0120	0.0000
Valine (mmol/l)	Branched-chain amino acids			whr	0.0078	0.0067	0.0089	0.0000
Valine (mmol/l)	Branched-chain amino acids			bf	0.0080	0.0070	0.0090	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids		children	bmi	0.0011	0.0008	0.0014	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			whr	0.0015	0.0012	0.0018	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			bf	0.0006	0.0003	0.0008	0.0001
Phenylalanine (mmol/l)	Aromatic amino acids		adolescents	bmi	0.0008	0.0005	0.0010	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			bf	0.0007	0.0003	0.0010	0.0001

Phenylalanine (mmol/l)	Aromatic amino acids	model1	young_adults	bmi	0.0013	0.0010	0.0015	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			whr	0.0008	0.0005	0.0011	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			bf	0.0008	0.0005	0.0011	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids		adults	bmi	0.0015	0.0013	0.0017	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			whr	0.0009	0.0007	0.0011	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			bf	0.0011	0.0009	0.0013	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids		children	bmi	0.0012	0.0009	0.0015	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			whr	0.0015	0.0012	0.0018	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			bf	0.0005	0.0002	0.0008	0.0031
Phenylalanine (mmol/l)	Aromatic amino acids		adolescents	bmi	0.0007	0.0004	0.0010	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			bf	0.0006	0.0002	0.0009	0.0015
Phenylalanine (mmol/l)	Aromatic amino acids		young_adults	bmi	0.0013	0.0010	0.0015	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			whr	0.0008	0.0006	0.0011	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			bf	0.0008	0.0005	0.0011	0.0000

Phenylalanine (mmol/l)	Aromatic amino acids	model2	adults	bmi	0.0015	0.0013	0.0017	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			whr	0.0008	0.0006	0.0010	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			bf	0.0011	0.0009	0.0013	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids	model3	adolescents	bmi	0.0006	0.0001	0.0011	0.0207
Phenylalanine (mmol/l)	Aromatic amino acids			bf	0.0006	0.0000	0.0012	0.0669
Phenylalanine (mmol/l)	Aromatic amino acids		young_adults	bmi	0.0015	0.0009	0.0021	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			whr	0.0009	0.0003	0.0015	0.0058
Phenylalanine (mmol/l)	Aromatic amino acids			bf	0.0007	0.0000	0.0014	0.0431
Phenylalanine (mmol/l)	Aromatic amino acids		adults	bmi	0.0015	0.0013	0.0017	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			whr	0.0009	0.0007	0.0011	0.0000
Phenylalanine (mmol/l)	Aromatic amino acids			bf	0.0012	0.0009	0.0014	0.0000
Tyrosine (mmol/l)	Aromatic amino acids		children	bmi	0.0021	0.0015	0.0026	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			whr	0.0018	0.0013	0.0024	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			bf	0.0013	0.0008	0.0019	0.0000

Tyrosine (mmol/l)	Aromatic amino acids	model1	adolescents	bmi	0.0018	0.0013	0.0023	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			bf	0.0019	0.0012	0.0025	0.0000
Tyrosine (mmol/l)	Aromatic amino acids		young_adults	bmi	0.0028	0.0024	0.0032	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			whr	0.0022	0.0018	0.0026	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			bf	0.0026	0.0022	0.0030	0.0000
Tyrosine (mmol/l)	Aromatic amino acids		adults	bmi	0.0033	0.0030	0.0037	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			whr	0.0022	0.0018	0.0026	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			bf	0.0025	0.0022	0.0029	0.0000
Tyrosine (mmol/l)	Aromatic amino acids		children	bmi	0.0021	0.0015	0.0027	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			whr	0.0019	0.0013	0.0024	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			bf	0.0011	0.0005	0.0017	0.0001
Tyrosine (mmol/l)	Aromatic amino acids		adolescents	bmi	0.0020	0.0014	0.0025	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			bf	0.0019	0.0013	0.0026	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			bmi	0.0030	0.0026	0.0034	0.0000

Tyrosine (mmol/l)	Aromatic amino acids	model2	young_adults	whr	0.0023	0.0019	0.0027	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			bf	0.0028	0.0024	0.0032	0.0000
Tyrosine (mmol/l)	Aromatic amino acids		adults	bmi	0.0034	0.0030	0.0038	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			whr	0.0022	0.0018	0.0026	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			bf	0.0026	0.0022	0.0030	0.0000
Tyrosine (mmol/l)	Aromatic amino acids	model3	adolescents	bmi	0.0012	0.0003	0.0022	0.0125
Tyrosine (mmol/l)	Aromatic amino acids			bf	0.0015	0.0002	0.0027	0.0218
Tyrosine (mmol/l)	Aromatic amino acids		young_adults	bmi	0.0035	0.0026	0.0044	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			whr	0.0020	0.0010	0.0029	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			bf	0.0028	0.0018	0.0039	0.0000
Tyrosine (mmol/l)	Aromatic amino acids		adults	bmi	0.0034	0.0030	0.0038	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			whr	0.0022	0.0018	0.0026	0.0000
Tyrosine (mmol/l)	Aromatic amino acids			bf	0.0026	0.0022	0.0030	0.0000
Alanine (mmol/l)	Amino acids			bmi	0.0016	-0.0005	0.0037	0.1362

Alanine (mmol/l)	Amino acids		children	whr	0.0073	0.0052	0.0094	0.0000
Alanine (mmol/l)	Amino acids			bf	-0.0011	-0.0032	0.0010	0.2889
Alanine (mmol/l)	Amino acids		adolescents	bmi	0.0032	0.0004	0.0059	0.0229
Alanine (mmol/l)	Amino acids			bf	0.0013	-0.0022	0.0048	0.4754
Alanine (mmol/l)	Amino acids		young_adults	bmi	0.0061	0.0038	0.0084	0.0000
Alanine (mmol/l)	Amino acids	model1		whr	0.0042	0.0016	0.0068	0.0014
Alanine (mmol/l)	Amino acids			bf	0.0064	0.0038	0.0090	0.0000
Alanine (mmol/l)	Amino acids		adults	bmi	0.0133	0.0112	0.0153	0.0000
Alanine (mmol/l)	Amino acids			whr	0.0108	0.0088	0.0128	0.0000
Alanine (mmol/l)	Amino acids			bf	0.0105	0.0085	0.0124	0.0000
Alanine (mmol/l)	Amino acids		children	bmi	0.0020	-0.0004	0.0045	0.1029
Alanine (mmol/l)	Amino acids			whr	0.0074	0.0052	0.0095	0.0000
Alanine (mmol/l)	Amino acids			bf	-0.0015	-0.0038	0.0008	0.2061
Alanine (mmol/l)	Amino acids			bmi	0.0037	0.0008	0.0066	0.0114

Alanine (mmol/l)	Amino acids		adolescents	bf	0.0015	-0.0022	0.0051	0.4235
Alanine (mmol/l)	Amino acids		young_adults	bmi	0.0070	0.0047	0.0093	0.0000
Alanine (mmol/l)	Amino acids	model2		whr	0.0048	0.0022	0.0074	0.0003
Alanine (mmol/l)	Amino acids			bf	0.0075	0.0048	0.0101	0.0000
Alanine (mmol/l)	Amino acids		adults	bmi	0.0133	0.0112	0.0154	0.0000
Alanine (mmol/l)	Amino acids			whr	0.0109	0.0088	0.0129	0.0000
Alanine (mmol/l)	Amino acids			bf	0.0104	0.0084	0.0124	0.0000
Alanine (mmol/l)	Amino acids		adolescents	bmi	0.0019	-0.0031	0.0069	0.4513
Alanine (mmol/l)	Amino acids			bf	0.0008	-0.0057	0.0072	0.8171
Alanine (mmol/l)	Amino acids		young_adults	bmi	0.0063	0.0007	0.0119	0.0272
Alanine (mmol/l)	Amino acids			whr	0.0010	-0.0045	0.0066	0.7147
Alanine (mmol/l)	Amino acids			bf	0.0072	0.0011	0.0134	0.0218
Alanine (mmol/l)	Amino acids			bmi	0.0136	0.0113	0.0159	0.0000
Alanine (mmol/l)	Amino acids			whr	0.0112	0.0090	0.0134	0.0000

Alanine (mmol/l)	Amino acids	model3	adults	bf	0.0108	0.0086	0.0131	0.0000
Glutamine (mmol/l)	Amino acids	model1	children	bmi	-0.0033	-0.0052	-0.0014	0.0007
Glutamine (mmol/l)	Amino acids			whr	0.0022	0.0003	0.0041	0.0263
Glutamine (mmol/l)	Amino acids			bf	-0.0053	-0.0071	-0.0034	0.0000
Glutamine (mmol/l)	Amino acids		adolescents	bmi	-0.0072	-0.0103	-0.0041	0.0000
Glutamine (mmol/l)	Amino acids			bf	-0.0089	-0.0128	-0.0049	0.0000
Glutamine (mmol/l)	Amino acids		young_adults	bmi	-0.0072	-0.0101	-0.0043	0.0000
Glutamine (mmol/l)	Amino acids			whr	-0.0058	-0.0091	-0.0025	0.0005
Glutamine (mmol/l)	Amino acids			bf	-0.0113	-0.0146	-0.0080	0.0000
Glutamine (mmol/l)	Amino acids		adults	bmi	-0.0087	-0.0106	-0.0068	0.0000
Glutamine (mmol/l)	Amino acids			whr	-0.0079	-0.0098	-0.0060	0.0000
Glutamine (mmol/l)	Amino acids			bf	-0.0080	-0.0098	-0.0061	0.0000
Glutamine (mmol/l)	Amino acids			bmi	-0.0037	-0.0059	-0.0015	0.0008
Glutamine (mmol/l)	Amino acids			whr	0.0022	0.0003	0.0041	0.0264

Glutamine (mmol/l)	Amino acids		children	bf	-0.0060	-0.0081	-0.0040	0.0000
Glutamine (mmol/l)	Amino acids		adolescents	bmi	-0.0072	-0.0104	-0.0039	0.0000
Glutamine (mmol/l)	Amino acids			bf	-0.0086	-0.0127	-0.0045	0.0000
Glutamine (mmol/l)	Amino acids		young_adults	bmi	-0.0070	-0.0099	-0.0041	0.0000
Glutamine (mmol/l)	Amino acids	model2		whr	-0.0054	-0.0087	-0.0021	0.0013
Glutamine (mmol/l)	Amino acids			bf	-0.0112	-0.0145	-0.0078	0.0000
Glutamine (mmol/l)	Amino acids		adults	bmi	-0.0093	-0.0112	-0.0074	0.0000
Glutamine (mmol/l)	Amino acids			whr	-0.0082	-0.0101	-0.0063	0.0000
Glutamine (mmol/l)	Amino acids			bf	-0.0085	-0.0104	-0.0066	0.0000
Glutamine (mmol/l)	Amino acids		adolescents	bmi	-0.0077	-0.0133	-0.0021	0.0070
Glutamine (mmol/l)	Amino acids			bf	-0.0077	-0.0149	-0.0005	0.0358
Glutamine (mmol/l)	Amino acids		young_adults	bmi	-0.0046	-0.0117	0.0026	0.2088
Glutamine (mmol/l)	Amino acids			whr	-0.0074	-0.0145	-0.0003	0.0413
Glutamine (mmol/l)	Amino acids			bf	-0.0101	-0.0180	-0.0023	0.0118

Glutamine (mmol/l)	Amino acids	model3	adults	bmi	-0.0092	-0.0113	-0.0071	0.0000
Glutamine (mmol/l)	Amino acids			whr	-0.0079	-0.0099	-0.0058	0.0000
Glutamine (mmol/l)	Amino acids			bf	-0.0086	-0.0106	-0.0066	0.0000
Histidine (mmol/l)	Amino acids	model1	children	bmi	0.0010	0.0006	0.0014	0.0000
Histidine (mmol/l)	Amino acids			whr	0.0007	0.0003	0.0011	0.0006
Histidine (mmol/l)	Amino acids			bf	0.0002	-0.0002	0.0006	0.3255
Histidine (mmol/l)	Amino acids		adolescents	bmi	0.0001	-0.0005	0.0007	0.6849
Histidine (mmol/l)	Amino acids			bf	0.0001	-0.0007	0.0009	0.7758
Histidine (mmol/l)	Amino acids		young_adults	bmi	-0.0002	-0.0005	0.0001	0.2562
Histidine (mmol/l)	Amino acids			whr	0.0000	-0.0004	0.0004	0.9882
Histidine (mmol/l)	Amino acids			bf	-0.0004	-0.0008	0.0000	0.0359
Histidine (mmol/l)	Amino acids		adults	bmi	-0.0009	-0.0013	-0.0005	0.0000
Histidine (mmol/l)	Amino acids			whr	-0.0003	-0.0006	0.0001	0.1743
Histidine (mmol/l)	Amino acids			bf	-0.0007	-0.0011	-0.0004	0.0001

Histidine (mmol/l)	Amino acids			bmi	0.0010	0.0005	0.0015	0.0000
Histidine (mmol/l)	Amino acids		children	whr	0.0007	0.0003	0.0011	0.0005
Histidine (mmol/l)	Amino acids			bf	0.0000	-0.0004	0.0005	0.9265
Histidine (mmol/l)	Amino acids		adolescents	bmi	0.0001	-0.0005	0.0008	0.7437
Histidine (mmol/l)	Amino acids			bf	0.0001	-0.0007	0.0009	0.8149
Histidine (mmol/l)	Amino acids			bmi	-0.0001	-0.0004	0.0002	0.5357
Histidine (mmol/l)	Amino acids	model2	young_adults	whr	0.0001	-0.0003	0.0004	0.6825
Histidine (mmol/l)	Amino acids			bf	-0.0003	-0.0007	0.0001	0.1148
Histidine (mmol/l)	Amino acids			bmi	-0.0008	-0.0012	-0.0004	0.0000
Histidine (mmol/l)	Amino acids		adults	whr	-0.0002	-0.0006	0.0002	0.3159
Histidine (mmol/l)	Amino acids			bf	-0.0007	-0.0010	-0.0003	0.0007
Histidine (mmol/l)	Amino acids		adolescents	bmi	0.0003	-0.0009	0.0015	0.6480
Histidine (mmol/l)	Amino acids			bf	0.0006	-0.0009	0.0022	0.4164
Histidine (mmol/l)	Amino acids			bmi	0.0003	-0.0005	0.0012	0.4404

Histidine (mmol/l)	Amino acids	model3	young_adults	whr	0.0002	-0.0006	0.0011	0.5957
Histidine (mmol/l)	Amino acids			bf	-0.0002	-0.0012	0.0008	0.6755
Histidine (mmol/l)	Amino acids		adults	bmi	-0.0006	-0.0010	-0.0002	0.0032
Histidine (mmol/l)	Amino acids			whr	-0.0001	-0.0006	0.0003	0.4868
Histidine (mmol/l)	Amino acids			bf	-0.0006	-0.0010	-0.0002	0.0064

A.4.3 Correlations

Due to the large number of tests performed, concordance between models, exposures, and age groups were investigated using Spearman's correlations.

```
[1] "Correlations across models within exposures and age groups"

[1] "Children BMI"

          model1    model2
model1 1.0000000 0.9552825
model2 0.9552825 1.0000000

[1] "Children WHR"

         model1   model2
model1 1.000000 0.999278
model2 0.999278 1.000000

[1] "Children BF"

          model1    model2
model1 1.0000000 0.9407415
model2 0.9407415 1.0000000

[1] "Adolescents BMI"
```

```
          model1    model2    model3
model1 1.0000000 0.9795601 0.9521372
model2 0.9795601 1.0000000 0.9741246
model3 0.9521372 0.9741246 1.0000000

[1] "Adolescents BF"

          model1    model2    model3
model1 1.0000000 0.9571041 0.9459728
model2 0.9571041 1.0000000 0.9418077
model3 0.9459728 0.9418077 1.0000000

[1] "Young adults BMI"

          model1    model2    model3
model1 1.0000000 0.9918482 0.8245953
model2 0.9918482 1.0000000 0.8143402
model3 0.8245953 0.8143402 1.0000000

[1] "Young adults WHR"

          model1    model2    model3
model1 1.0000000 0.9992526 0.9606961
model2 0.9992526 1.0000000 0.9594533
model3 0.9606961 0.9594533 1.0000000
```

```
[1] "Young adults BF"

          model1    model2    model3
model1 1.0000000 0.9923692 0.8796946
model2 0.9923692 1.0000000 0.8642943
model3 0.8796946 0.8642943 1.0000000

[1] "Adults BMI"

          model1    model2    model3
model1 1.0000000 0.9760175 0.9650574
model2 0.9760175 1.0000000 0.9947999
model3 0.9650574 0.9947999 1.0000000

[1] "Adults WHR"

          model1    model2    model3
model1 1.0000000 0.9982737 0.9517970
model2 0.9982737 1.0000000 0.9554885
model3 0.9517970 0.9554885 1.0000000

[1] "Adults BF"

          model1    model2    model3
model1 1.0000000 0.9945195 0.9771555
```

```
model2 0.9945195 1.0000000 0.9850295
model3 0.9771555 0.9850295 1.0000000

[1] "Correlations across exposures within age groups for model 2"

[1] "Children"

           bf       bmi       whr
bf  1.0000000 0.8914358 0.6066604
bmi 0.8914358 1.0000000 0.7711406
whr 0.6066604 0.7711406 1.0000000

[1] "Adolescents"

           bf       bmi
bf  1.0000000 0.9377422
bmi 0.9377422 1.0000000

[1] "Young adults"

           bf       bmi       whr
bf  1.0000000 0.9659641 0.8012407
bmi 0.9659641 1.0000000 0.8123532
whr 0.8012407 0.8123532 1.0000000

[1] "Adults"
```

```
           bf       bmi       whr
bf  1.0000000 0.9179145 0.9542118
bmi 0.9179145 1.0000000 0.9366665
whr 0.9542118 0.9366665 1.0000000

[1] "Correlations within exposures across age groups for model 2"

[1] "BMI"

             adolescents    adults  children young_adults
adolescents    1.0000000 0.4808187 0.7695565    0.7356921
adults         0.4808187 1.0000000 0.5592282    0.6902187
children       0.7695565 0.5592282 1.0000000    0.7299576
young_adults   0.7356921 0.6902187 0.7299576    1.0000000

[1] "WHR"

                adults  children young_adults
adults       1.0000000 0.5473523    0.7357566
children     0.5473523 1.0000000    0.5023414
young_adults 0.7357566 0.5023414    1.0000000

[1] "BF"

             adolescents    adults  children young_adults
adolescents    1.0000000 0.5328382 0.8151367    0.6930515
```

adults	0.5328382	1.0000000	0.5135602	0.7160939
children	0.8151367	0.5135602	1.0000000	0.7088497
young_adults	0.6930515	0.7160939	0.7088497	1.0000000

A.4.4 Communications

From: **Simon Wilkinson** simon.wilkinson@tanita.eu
Subject: Tanita TBF 305
Date: 8 April 2020 at 09:30
To: matthew.lee@bristol.ac.uk

Good morning Matt,

Apologies nobody has come back to you on this, like most places we are down to a skeleton staff at HQ in Amsterdam.

We have received communication from Tokyo HQ that unfortunately it is not possible to convert the impedance values only into a body fat percentage from a manual input, this would have required software to be utilised at the point of measurement.

If there is anything else I might be able to help with, just let me know.

--
Healthy regards

Simon Wilkinson
Technical Rep Fitness & Sport

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Figure A.1: Email communication with Tanita RE calculation of body fat percentage from raw impedance

A.4.5 Figures

Forestplots

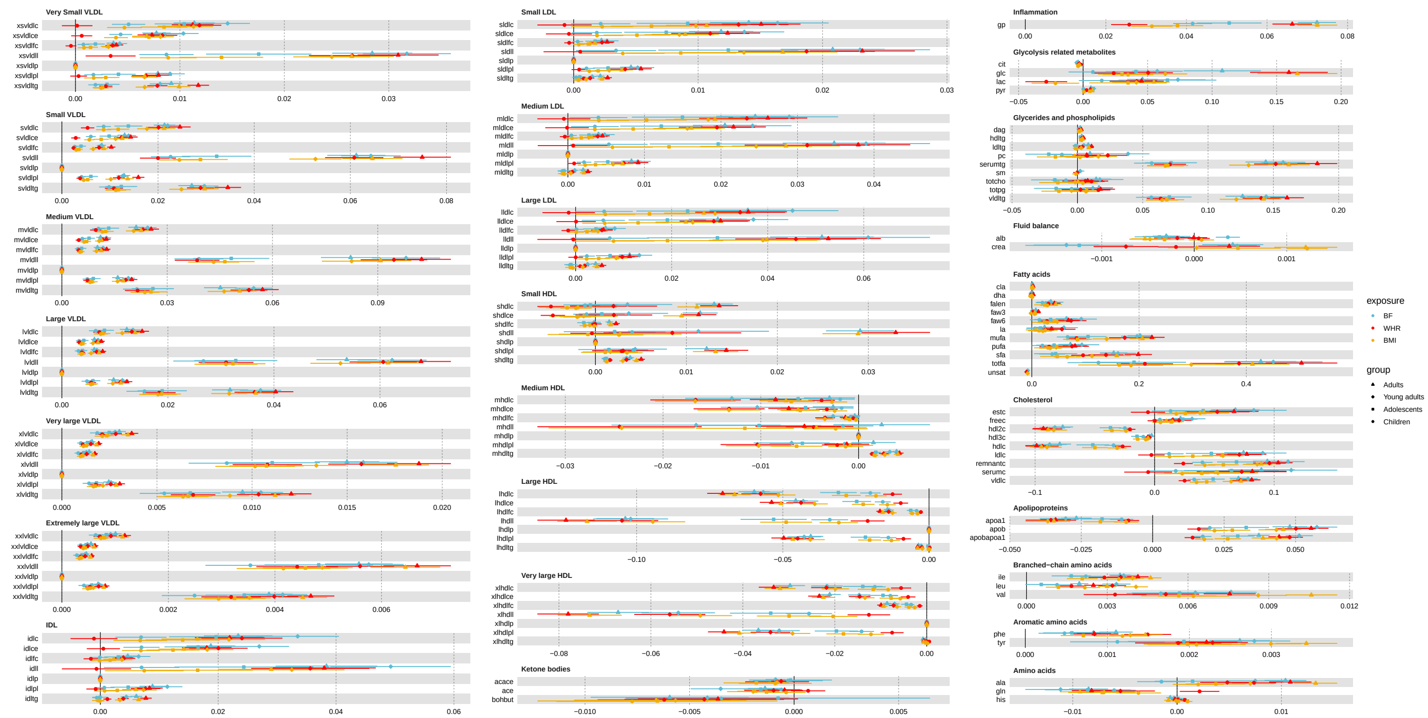

Figure A.2: Forestplot of effect estimates from a linear regression

Figure A.2 shows effect estimates and 95% confidence intervals from model 2 for all exposures and age groups. Effect estimates are per-standard deviation increase in metabolite per-standard deviation increase in exposure.

Figure A.3: Forestplot of effect estimates from a linear regression, derived metabolites

Figure A.3 shows effect estimates and 95% confidence intervals from model 2 for all exposures and age groups. Effect estimates are *per-standard deviation increase in metabolite per-standard deviation increase in exposure.*

Forestplots show the effect estimate and 95% confidence interval with multiple testing thresholds (solid points) set as the number of independent metabolites for each age group.

Circos plots

Circos plots show effect estimates and 95% confidence intervals with multiple testing thresholds (solid points) set as the number of independent metabolites for each age group (set as the lowest number of independent metabolites for combined age group plots).

Figure A.4: Circos plot of effect estimates from a linear regression in ALSPAC children, supplementary metabolites

Comparison of metabolic profile across exposures for each age group *Figure A.4 shows effect estiamtes and 95% confidence intervals from a linear regression. Each point represents a single result, with the metabolites labelled around the outside and each track representing an exposure; the outer track is BMI, the middle track is WHR, the inner track is BF. Solid points indicate a multiple testing threshold has been reached. BMI =*

body mass index; WHR = waist hip ratio; FFM = fat free mass.

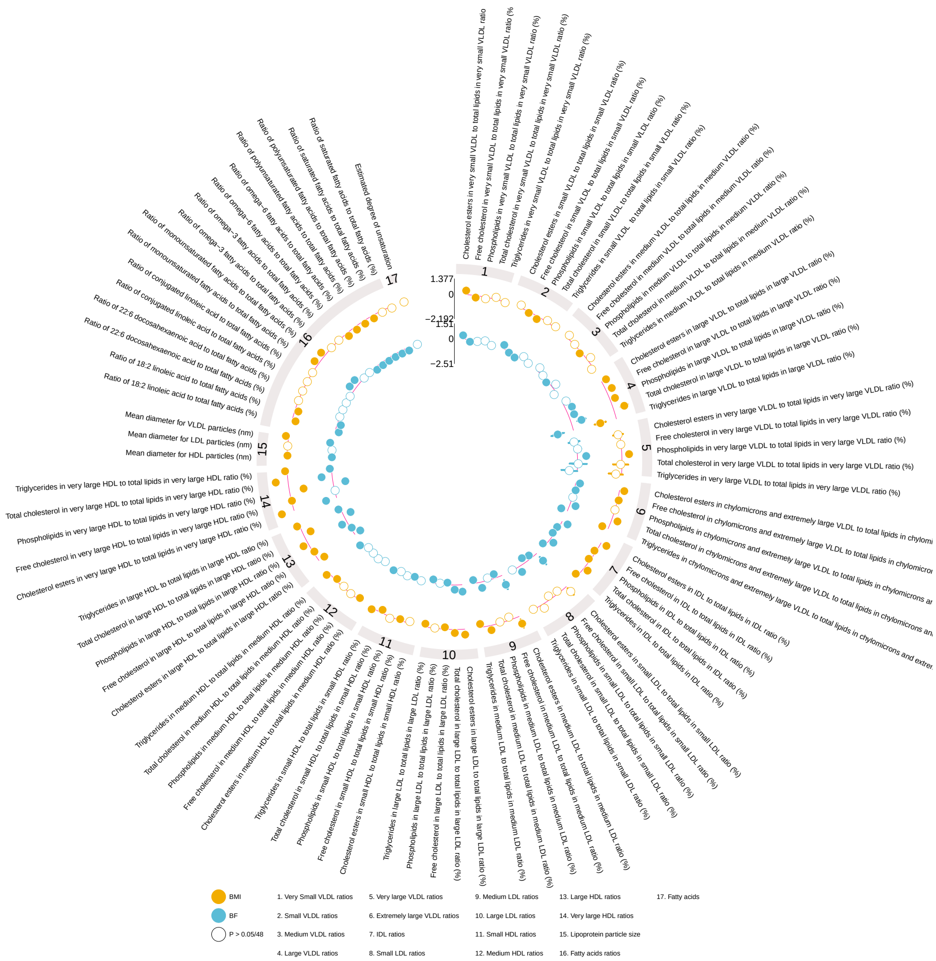

Figure A.5: Circos plot of effect estimates from a linear regression in ALSPAC adolescents, supplementary metabolites

Figure A.5 shows effect estiamtes and 95% confidence intervals from a linear regression. Each point represents a single result, with the metabolites labelled around the outside and each track representing an exposure; the outer track is BMI, the middle track is BF. Solid points indicate a multiple testing threshold has been reached. BMI = body mass index; BF = body fat percentage.

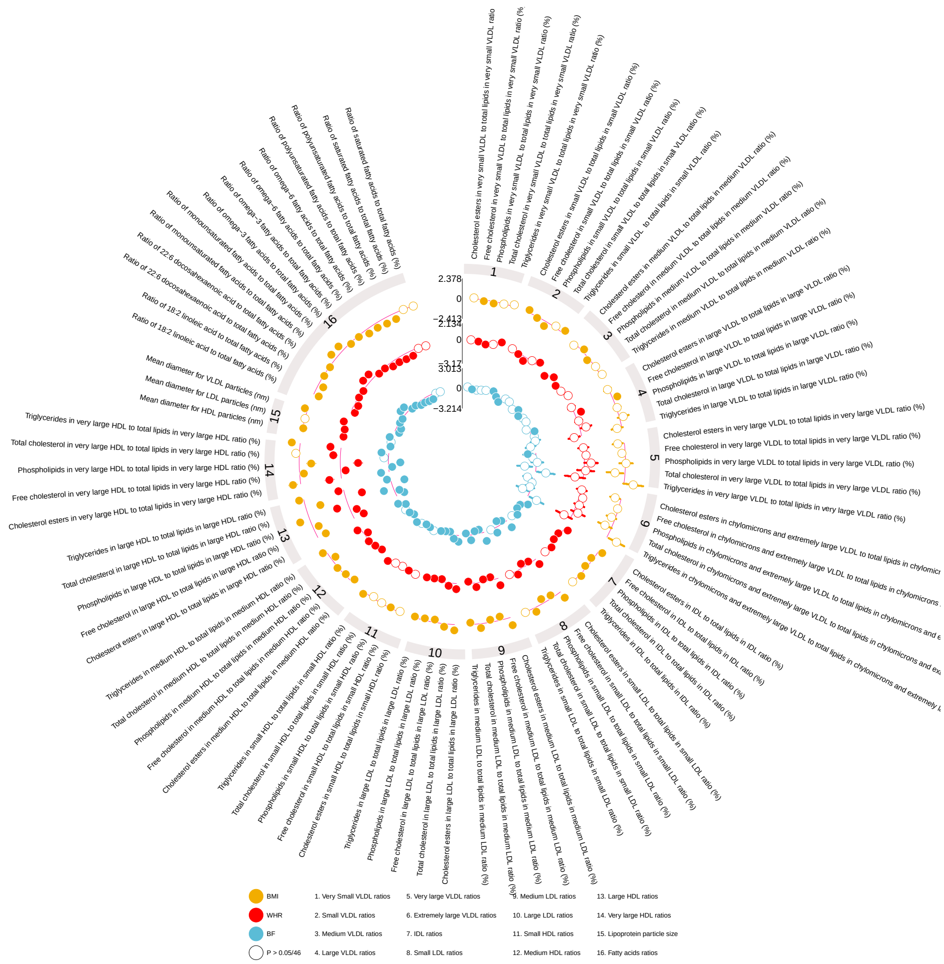

Figure A.6: Circos plot of effect estimates from a linear regression in ALSPAC young adults, supplementary metabolites

Figure A.6 shows effect estiamtes and 95% confidence intervals from a linear regression. Each point represents a single result, with the metabolites labelled around the outside and each track representing an exposure; the outer track is BMI, the middle track is WHR, the inner track is BF. Solid points indicate a multiple testing threshold has been reached. BMI = body mass index; WHR = waist hip ratio; BF = body fat percentage.

Figure A.7: Circos plot of effect estimates from a linear regression in ALSPAC adults, supplementary metabolites

Figure A.7 shows effect estiamtes and 95% confidence intervals from a linear regression. Each point represents a single result, with the metabolites labelled around the outside and each track representing an exposure; the outer track is BMI, the middle track is WHR, the inner track is BF. Solid points indicate a multiple testing threshold has been reached. BMI = body mass index; WHR = waist hip ratio; BF = body fat percentage.

A.5 Chapter 5

Table A.4: Metabolites from Kettunen et al (2016) used as outcomes in MR analysis

Abbreviation	Label	Class	subclass
ala	Alanine (mmol/l)	Amino acids	Amino acids
gln	Glutamine (mmol/l)	Amino acids	Amino acids
his	Histidine (mmol/l)	Amino acids	Amino acids
ile	Isoleucine (mmol/l)	Amino acids	Branched-chain amino acids
leu	Leucine (mmol/l)	Amino acids	Branched-chain amino acids
phe	Phenylalanine (mmol/l)	Amino acids	Aromatic amino acids
tyr	Tyrosine (mmol/l)	Amino acids	Aromatic amino acids
val	Valine (mmol/l)	Amino acids	Branched-chain amino acids
	Urea	Amino acids	Amino acids
apoa1	Apolipoprotein A-I (g/l)	Apolipoproteins	Apolipoproteins
apob	Apolipoprotein B (g/l)	Apolipoproteins	Apolipoproteins

estc	Esterified cholesterol (mmol/l)	Cholesterol	Cholesterol
freec	Free cholesterol (mmol/l)	Cholesterol	Cholesterol
hdlc	Total cholesterol in HDL (mmol/l)	Cholesterol	Cholesterol
ldlc	Total cholesterol in LDL (mmol/l)	Cholesterol	Cholesterol
serumc	Serum total cholesterol (mmol/l)	Cholesterol	Cholesterol
dha	22:6, docosahexaenoic acid (mmol/l)	Fatty acids	Fatty acids
falen	Estimated description of fatty acid chain length, not actual carbon number	Fatty acids	Fatty acids
faw3	Omega-3 fatty acids (mmol/l)	Fatty acids	Fatty acids
faw6	Omega-6 fatty acids (mmol/l)	Fatty acids	Fatty acids
la	18:2, linoleic acid (mmol/l)	Fatty acids	Fatty acids

mufa	Monounsaturated fatty acids; 16:1, 18:1 (mmol/l)	Fatty acids	Fatty acids
totfa	Total fatty acids (mmol/l)	Fatty acids	Fatty acids
	Average number of double bonds in a fatty acid chain	Fatty acids	Fatty acids
	Average number of methylene groups in a fatty acid chain	Fatty acids	Fatty acids
	Omega-7, omega-9 and saturated fatty acids	Fatty acids	Fatty acids
	Other polyunsaturated fatty acids than 18:2	Fatty acids	Fatty acids
	Ratio of bisallylic groups to total fatty acids	Fatty acids	Fatty acids
alb	Albumin (signal area)	Fluid balance	Fluid balance
crea	Creatinine (mmol/l)	Fluid balance	Fluid balance
pc	Phosphatidylcholine and other cholines (mmol/l)	Glycerides and phospholipids	Glycerides and phospholipids

serumtg	Serum total triglycerides (mmol/l)	Glycerides and phospholipids	Glycerides and phospholipids
sm	Sphingomyelins (mmol/l)	Glycerides and phospholipids	Glycerides and phospholipids
totpg	Total phosphoglycerides (mmol/l)	Glycerides and phospholipids	Glycerides and phospholipids
cit	Citrate (mmol/l)	Glycolysis related metabolites	Glycolysis related metabolites
glc	Glucose (mmol/l)	Glycolysis related metabolites	Glycolysis related metabolites
glol	Glycerol (mmol/l)	Glycolysis related metabolites	Glycolysis related metabolites
lac	Lactate (mmol/l)	Glycolysis related metabolites	Glycolysis related metabolites
pyr	Pyruvate (mmol/l)	Glycolysis related metabolites	Glycolysis related metabolites
gp	Glycoprotein acetyls, mainly a1-acid glycoprotein (mmol/l)	Inflammation	Inflammation

acace	Acetoacetate (mmol/l)	Ketone bodies	Ketone bodies
ace	Acetate (mmol/l)	Ketone bodies	Ketone bodies
bohbut	3-hydroxybutyrate (mmol/l)	Ketone bodies	Ketone bodies
hdld	Mean diameter for HDL particles (nm)	Lipoprotein particle size	Lipoprotein particle size
ldld	Mean diameter for LDL particles (nm)	Lipoprotein particle size	Lipoprotein particle size
vldld	Mean diameter for VLDL particles (nm)	Lipoprotein particle size	Lipoprotein particle size
idlc	Total cholesterol in IDL (mmol/l)	Lipoprotein subclasses	IDL
idlfc	Free cholesterol in IDL (mmol/l)	Lipoprotein subclasses	IDL
idll	Total lipids in IDL (mmol/l)	Lipoprotein subclasses	IDL
idlp	Concentration of IDL particles (mol/l)	Lipoprotein subclasses	IDL
idlpl	Phospholipids in IDL (mmol/l)	Lipoprotein subclasses	IDL

idltg	Triglycerides in IDL (mmol/l)	Lipoprotein subclasses	IDL
lhdlc	Total cholesterol in large HDL (mmol/l)	Lipoprotein subclasses	Large HDL
lhdlce	Cholesterol esters in large HDL (mmol/l)	Lipoprotein subclasses	Large HDL
lhdlfc	Free cholesterol in large HDL (mmol/l)	Lipoprotein subclasses	Large HDL
lhdll	Total lipids in large HDL (mmol/l)	Lipoprotein subclasses	Large HDL
lhdlp	Concentration of large HDL particles (mol/l)	Lipoprotein subclasses	Large HDL
lhdlpl	Phospholipids in large HDL (mmol/l)	Lipoprotein subclasses	Large HDL
lldlc	Total cholesterol in large LDL (mmol/l)	Lipoprotein subclasses	Large LDL
lldlce	Cholesterol esters in large LDL (mmol/l)	Lipoprotein subclasses	Large LDL

lldlfc	Free cholesterol in large LDL (mmol/l)	Lipoprotein subclasses	Large LDL
lldll	Total lipids in large LDL (mmol/l)	Lipoprotein subclasses	Large LDL
lldlp	Concentration of large LDL particles (mol/l)	Lipoprotein subclasses	Large LDL
lldlpl	Phospholipids in large LDL (mmol/l)	Lipoprotein subclasses	Large LDL
lvldlc	Total cholesterol in large VLDL (mmol/l)	Lipoprotein subclasses	Large VLDL
lvldlce	Cholesterol esters in large VLDL (mmol/l)	Lipoprotein subclasses	Large VLDL
lvldlfc	Free cholesterol in large VLDL (mmol/l)	Lipoprotein subclasses	Large VLDL
lvldll	Total lipids in large VLDL (mmol/l)	Lipoprotein subclasses	Large VLDL
lvldlp	Concentration of large VLDL particles (mol/l)	Lipoprotein subclasses	Large VLDL

lvldlpl	Phospholipids in large VLDL (mmol/l)	Lipoprotein subclasses	Large VLDL
lvldltg	Triglycerides in large VLDL (mmol/l)	Lipoprotein subclasses	Large VLDL
mhdlc	Total cholesterol in medium HDL (mmol/l)	Lipoprotein subclasses	Medium HDL
mhdlce	Cholesterol esters in medium HDL (mmol/l)	Lipoprotein subclasses	Medium HDL
mhdlfc	Free cholesterol in medium HDL (mmol/l)	Lipoprotein subclasses	Medium HDL
mhdll	Total lipids in medium HDL (mmol/l)	Lipoprotein subclasses	Medium HDL
mhdlp	Concentration of medium HDL particles (mol/l)	Lipoprotein subclasses	Medium HDL
mhdlpl	Phospholipids in medium HDL (mmol/l)	Lipoprotein subclasses	Medium HDL
mldlc	Total cholesterol in medium LDL (mmol/l)	Lipoprotein subclasses	Medium LDL

mldlce	Cholesterol esters in medium LDL (mmol/l)	Lipoprotein subclasses	Medium LDL
mldll	Total lipids in medium LDL (mmol/l)	Lipoprotein subclasses	Medium LDL
mldlp	Concentration of medium LDL particles (mol/l)	Lipoprotein subclasses	Medium LDL
mldlpl	Phospholipids in medium LDL (mmol/l)	Lipoprotein subclasses	Medium LDL
mvldlc	Total cholesterol in medium VLDL (mmol/l)	Lipoprotein subclasses	Medium VLDL
mvldlce	Cholesterol esters in medium VLDL (mmol/l)	Lipoprotein subclasses	Medium VLDL
mvldlfc	Free cholesterol in medium VLDL (mmol/l)	Lipoprotein subclasses	Medium VLDL
mvldll	Total lipids in medium VLDL (mmol/l)	Lipoprotein subclasses	Medium VLDL
mvldlp	Concentration of medium VLDL particles (mol/l)	Lipoprotein subclasses	Medium VLDL

mvldlpl	Phospholipids in medium VLDL (mmol/l)	Lipoprotein subclasses	Medium VLDL
mvldltg	Triglycerides in medium VLDL (mmol/l)	Lipoprotein subclasses	Medium VLDL
shdll	Total lipids in small HDL (mmol/l)	Lipoprotein subclasses	Small HDL
shdlp	Concentration of small HDL particles (mol/l)	Lipoprotein subclasses	Small HDL
shdltg	Triglycerides in small HDL (mmol/l)	Lipoprotein subclasses	Small HDL
sldlc	Total cholesterol in small LDL (mmol/l)	Lipoprotein subclasses	Small LDL
sldll	Total lipids in small LDL (mmol/l)	Lipoprotein subclasses	Small LDL
sldlp	Concentration of small LDL particles (mol/l)	Lipoprotein subclasses	Small LDL
svldlc	Total cholesterol in small VLDL (mmol/l)	Lipoprotein subclasses	Small VLDL

svldlfc	Free cholesterol in small VLDL (mmol/l)	Lipoprotein subclasses	Small VLDL
svldll	Total lipids in small VLDL (mmol/l)	Lipoprotein subclasses	Small VLDL
svldlp	Concentration of small VLDL particles (mol/l)	Lipoprotein subclasses	Small VLDL
svldlpl	Phospholipids in small VLDL (mmol/l)	Lipoprotein subclasses	Small VLDL
svldltg	Triglycerides in small VLDL (mmol/l)	Lipoprotein subclasses	Small VLDL
xlhdlc	Total cholesterol in very large HDL (mmol/l)	Lipoprotein subclasses	Very large HDL
xlhdlce	Cholesterol esters in very large HDL (mmol/l)	Lipoprotein subclasses	Very large HDL
xlhdlfc	Free cholesterol in very large HDL (mmol/l)	Lipoprotein subclasses	Very large HDL
xlhdll	Total lipids in very large HDL (mmol/l)	Lipoprotein subclasses	Very large HDL

xlhdlp	Concentration of very large HDL particles (mol/l)	Lipoprotein subclasses	Very large HDL
xlhdlpl	Phospholipids in very large HDL (mmol/l)	Lipoprotein subclasses	Very large HDL
xlhdltg	Triglycerides in very large HDL (mmol/l)	Lipoprotein subclasses	Very large HDL
xlvldll	Total lipids in very large VLDL (mmol/l)	Lipoprotein subclasses	Very large VLDL
xlvldlp	Concentration of very large VLDL particles (mol/l)	Lipoprotein subclasses	Very large VLDL
xlvldlpl	Phospholipids in very large VLDL (mmol/l)	Lipoprotein subclasses	Very large VLDL
xlvldltg	Triglycerides in very large VLDL (mmol/l)	Lipoprotein subclasses	Very large VLDL
xsvldll	Total lipids in very small VLDL (mmol/l)	Lipoprotein subclasses	Very Small VLDL
xsvldlp	Concentration of very small VLDL particles (mol/l)	Lipoprotein subclasses	Very Small VLDL

xsvldlpl	Phospholipids in very small VLDL (mmol/l)	Lipoprotein subclasses	Very Small VLDL
xsvldltg	Triglycerides in very small VLDL (mmol/l)	Lipoprotein subclasses	Very Small VLDL
xxlvldll	Total lipids in chylomicrons and extremely large VLDL (mmol/l)	Lipoprotein subclasses	Extremely large VLDL
xxlvldlp	Concentration of chylomicrons and extremely large VLDL particles (mol/l)	Lipoprotein subclasses	Extremely large VLDL
xxlvldlpl	Phospholipids in chylomicrons and extremely large VLDL (mmol/l)	Lipoprotein subclasses	Extremely large VLDL

xxlvldltg	Triglycerides in chylomicrons and extremely large VLDL (mmol/l)	Lipoprotein subclasses	Extremely large VLDL
	Average number of methylene groups per double bond	Metabolites ratio	Metabolites ratio
	Ratio of bisallylic groups to double bonds	Metabolites ratio	Metabolites ratio
	Glycoproteins	Protein	Protein

Table A.5: Genetic instrumental variables

SNP	Chr	BP	EA	NEA	EAF	B	SE	P	Exp	Ref	Note	Clump
rs41279738	1	110082551	g	t	0.025	0.388	0.065	2.72e-09	BF	Hubel		No
rs11205303	1	149906413	c	t	0.398	0.137	0.021	6.77e-11	BF	Hubel		No
rs543874	1	177889480	g	a	0.205	0.252	0.026	8.26e-23	BF	Hubel		No
rs2644109	1	201797535	c	t	0.669	-0.120	0.022	4.73e-08	BF	Hubel		No
rs2820444	1	219741820	g	a	0.709	-0.140	0.023	6.66e-10	BF	Hubel		No
rs12140153	1	62579891	g	t	0.909	0.214	0.036	3.35e-09	BF	Hubel		No
rs11209948	1	72811904	g	t	0.394	-0.116	0.021	3.59e-08	BF	Hubel		No
rs71658797	1	77967507	t	a	0.884	-0.179	0.032	2.17e-08	BF	Hubel		Yes
rs159962	1	8490983	c	t	0.665	-0.119	0.022	4.47e-08	BF	Hubel		No
rs1128249	2	165528624	g	t	0.606	-0.151	0.021	9.03e-13	BF	Hubel		No
rs10930502	2	172890588	g	a	0.302	-0.134	0.023	2.81e-09	BF	Hubel		Yes
rs7590658	2	205375133	g	a	0.078	0.251	0.040	4.12e-10	BF	Hubel		No
rs2972138	2	227106217	g	a	0.654	-0.120	0.022	2.7e-08	BF	Hubel		No
rs59086897	2	25145173	t	a	0.506	-0.193	0.021	1.33e-20	BF	Hubel		No

rs13410783	2	36789166	g	a	0.365	0.127	0.022	3.14e-09	BF	Hubel	No
rs62104180	2	466003	g	a	0.952	0.350	0.047	1.17e-13	BF	Hubel	No
rs6545714	2	59307725	g	a	0.394	0.144	0.021	1.09e-11	BF	Hubel	No
rs4410328	2	69600683	c	t	0.589	0.117	0.021	2.58e-08	BF	Hubel	No
rs11712037	3	12344730	g	c	0.116	0.270	0.032	2.44e-17	BF	Hubel	No
rs1464419	3	153691260	c	a	0.328	-0.122	0.022	2.89e-08	BF	Hubel	No
rs3749237	3	49770032	g	a	0.681	-0.135	0.022	9.86e-10	BF	Hubel	No
rs9818550	3	61271329	g	t	0.286	-0.130	0.023	2.32e-08	BF	Hubel	No
rs13107325	4	103188709	c	t	0.928	-0.266	0.040	1.77e-11	BF	Hubel	No
rs2192527	4	18329824	g	a	0.471	0.134	0.021	9.68e-11	BF	Hubel	No
rs13130484	4	45175691	c	t	0.572	-0.200	0.021	1.41e-21	BF	Hubel	No
rs6847975	4	80812960	g	a	0.650	-0.137	0.022	2.55e-10	BF	Hubel	No
rs2963469	5	158001309	t	a	0.357	-0.140	0.022	1.7e-10	BF	Hubel	No
rs13163173	5	87943620	c	a	0.834	-0.186	0.028	5.72e-11	BF	Hubel	No
rs1591805	6	126717064	g	a	0.501	-0.120	0.021	8.21e-09	BF	Hubel	No
rs62396185	6	26180634	g	c	0.739	0.184	0.024	6.3e-15	BF	Hubel	No

rs1046080	6	31595882	c	a	0.276	-0.128	0.023	2.73e-08	BF	Hubel	Yes
rs142550007	6	40267936	g	a	0.983	-0.445	0.081	3.6e-08	BF	Hubel	No
rs4711961	6	50833084	g	a	0.831	-0.165	0.028	2.41e-09	BF	Hubel	No
rs9320823	6	98429337	c	t	0.609	0.134	0.021	2.26e-10	BF	Hubel	No
rs35682716	7	113021580	c	t	0.654	0.120	0.022	4.49e-08	BF	Hubel	No
rs972283	7	130466854	g	a	0.522	-0.123	0.021	2.71e-09	BF	Hubel	No
rs80206917	7	140159389	c	t	0.287	-0.125	0.023	3.89e-08	BF	Hubel	No
rs848457	7	77602503	g	t	0.383	0.121	0.021	1.21e-08	BF	Hubel	No
rs7845090	8	73449940	g	a	0.297	0.142	0.023	6.72e-10	BF	Hubel	No
rs4744546	9	136924744	c	t	0.558	0.123	0.021	3.85e-09	BF	Hubel	No
rs11515071	9	15855545	c	t	0.642	0.169	0.022	4.37e-15	BF	Hubel	No
rs10968577	9	28415512	c	t	0.681	-0.131	0.022	2.76e-09	BF	Hubel	No
rs10749233	10	118777998	g	c	0.256	0.137	0.024	2.08e-08	BF	Hubel	No
rs12253527	10	21819824	g	a	0.679	-0.127	0.022	1.11e-08	BF	Hubel	No
rs10999439	10	72386740	c	t	0.270	0.144	0.023	5.65e-10	BF	Hubel	No
rs2274224	10	96039597	g	c	0.562	0.168	0.021	7.93e-16	BF	Hubel	No
rs11223600	11	133718882	c	t	0.906	0.203	0.035	1.05e-08	BF	Hubel	No

rs61888762	11	27709630	g	c	0.316	0.155	0.022	2.66e-12	BF	Hubel	No
rs10838137	11	43634973	c	a	0.666	-0.135	0.022	9.59e-10	BF	Hubel	No
rs59360790	11	47669175	c	t	0.400	0.176	0.021	6.31e-17	BF	Hubel	No
rs1426371	12	108629780	g	a	0.742	0.171	0.024	6.71e-13	BF	Hubel	No
rs7133378	12	124409502	g	a	0.679	-0.163	0.022	2.95e-13	BF	Hubel	No
rs7975788	12	90273927	g	t	0.264	0.132	0.023	1.39e-08	BF	Hubel	No
rs1928496	13	31012904	c	t	0.256	-0.131	0.024	3.32e-08	BF	Hubel	No
rs61969510	13	86484025	c	t	0.273	0.134	0.023	8.4e-09	BF	Hubel	No
rs7339274	13	99120272	c	t	0.715	0.144	0.023	2.06e-10	BF	Hubel	No
rs8021531	14	75737909	g	a	0.711	-0.127	0.023	2.85e-08	BF	Hubel	No
rs55882426	14	94120712	c	t	0.498	-0.116	0.021	2.54e-08	BF	Hubel	No
rs3751585	15	51741056	g	a	0.803	-0.143	0.026	3.11e-08	BF	Hubel	No
rs28399271	15	67710011	g	a	0.735	0.155	0.024	4.58e-11	BF	Hubel	No
rs8031704	15	84651185	c	a	0.669	-0.170	0.022	1.26e-14	BF	Hubel	No
rs2411453	16	28632021	g	t	0.595	-0.190	0.021	2.59e-19	BF	Hubel	No
rs879620	16	4015729	c	t	0.402	-0.135	0.021	2.03e-10	BF	Hubel	No
rs1421085	16	53800954	c	t	0.394	0.319	0.021	1.03e-51	BF	Hubel	No

rs11866219	16	69549749	c	a	0.576	-0.137	0.021	1.34e-10	BF	Hubel	No
rs2941318	16	9312782	g	a	0.579	0.114	0.021	4.74e-08	BF	Hubel	Yes
rs9893756	17	42321109	c	t	0.698	-0.142	0.023	4.1e-10	BF	Hubel	No
rs2080090	17	65828371	t	a	0.808	-0.164	0.027	6.17e-10	BF	Hubel	No
rs1834144	18	40744790	c	a	0.624	0.120	0.022	2.55e-08	BF	Hubel	No
rs663640	18	57846077	c	t	0.778	-0.176	0.025	2.1e-12	BF	Hubel	No
rs11666808	19	18383506	c	t	0.630	-0.179	0.021	6.06e-17	BF	Hubel	No
rs33823	19	34000725	c	t	0.360	-0.142	0.022	8.41e-11	BF	Hubel	No
rs1800437	19	46181392	g	c	0.808	0.151	0.026	6.91e-09	BF	Hubel	No
rs1538482	20	47705496	c	t	0.308	-0.139	0.022	6.3e-10	BF	Hubel	No
rs7282639	21	46491155	g	c	0.322	0.121	0.022	4.81e-08	BF	Hubel	No
rs4821764	22	38599364	g	a	0.422	0.151	0.021	6.43e-13	BF	Hubel	No
rs6728726	2	613976	C	T	0.840	0.037	0.007	2.9e-08	BF	Lu	No
rs693839	13	79856289	C	T	0.310	0.030	0.005	9.3e-09	BF	Lu	No
rs1558902	16	52361075	A	T	0.410	0.051	0.005	1.1e-25	BF	Lu	No
rs9906944	17	44446419	C	T	0.660	0.035	0.006	1.9e-08	BF	Lu	No

rs6857	19	50084094	C	T	0.830	0.053	0.009	6.8e-10	BF	Lu		No
rs6738627	2	165252696	A	G	0.370	0.030	0.005	1.8e-08	BF	Lu	FA SNP	No
rs2943650	2	226814165	C	T	0.370	0.037	0.006	3.6e-10	BF	Lu	FA SNP	No
rs17024393	1	109956211	C	T	0.040	0.066	0.009	7.03e-14	BMI	Locke		No
rs543874	1	176156103	G	A	0.193	0.048	0.004	2.62e-35	BMI	Locke		No
rs2820292	1	200050910	C	A	0.555	0.020	0.003	1.83e-10	BMI	Locke		No
rs657452	1	49362434	A	G	0.394	0.023	0.003	5.48e-13	BMI	Locke		No
rs11583200	1	50332407	C	T	0.396	0.018	0.003	1.48e-08	BMI	Locke		Yes
rs3101336	1	72523773	C	T	0.613	0.033	0.003	2.66e-26	BMI	Locke		No
rs12566985	1	74774781	G	A	0.446	0.024	0.003	3.28e-15	BMI	Locke		Yes
rs12401738	1	78219349	A	G	0.352	0.021	0.003	1.15e-10	BMI	Locke		No
rs11165643	1	96696685	T	C	0.583	0.022	0.003	2.07e-12	BMI	Locke		No
rs2121279	2	142759755	T	C	0.152	0.025	0.004	2.31e-08	BMI	Locke		No
rs1528435	2	181259207	T	C	0.631	0.018	0.003	1.2e-08	BMI	Locke		No
rs7599312	2	213121476	G	A	0.724	0.022	0.003	1.17e-10	BMI	Locke		No
rs10182181	2	25003800	G	A	0.462	0.031	0.003	8.78e-24	BMI	Locke		No
rs11126666	2	26782315	A	G	0.283	0.021	0.003	1.33e-09	BMI	Locke		Yes

rs1016287	2	59159129	T	C	0.287	0.023	0.003	2.25e-11	BMI	Locke	No
rs13021737	2	622348	G	A	0.828	0.060	0.004	1.11e-50	BMI	Locke	No
rs11688816	2	62906552	G	A	0.525	0.017	0.003	1.89e-08	BMI	Locke	Yes
rs16851483	3	142758126	T	G	0.066	0.048	0.008	3.55e-10	BMI	Locke	No
rs1516725	3	187306698	C	T	0.872	0.045	0.005	1.89e-22	BMI	Locke	No
rs6804842	3	25081441	G	A	0.575	0.019	0.003	2.48e-09	BMI	Locke	No
rs2365389	3	61211502	C	T	0.582	0.020	0.003	1.63e-10	BMI	Locke	No
rs3849570	3	81874802	A	C	0.359	0.019	0.003	2.6e-08	BMI	Locke	No
rs13078960	3	85890280	G	T	0.196	0.030	0.004	1.74e-14	BMI	Locke	No
rs13107325	4	103407732	T	C	0.072	0.048	0.007	1.83e-12	BMI	Locke	No
rs11727676	4	145878514	T	C	0.910	0.036	0.006	2.55e-08	BMI	Locke	No
rs10938397	4	44877284	G	A	0.434	0.040	0.003	3.21e-38	BMI	Locke	No
rs17001654	4	77348592	G	C	0.153	0.031	0.005	7.76e-09	BMI	Locke	No
rs2112347	5	75050998	T	G	0.629	0.026	0.003	6.19e-17	BMI	Locke	No
rs9400239	6	109084356	C	T	0.688	0.019	0.003	1.61e-08	BMI	Locke	No
rs13191362	6	162953340	A	G	0.879	0.028	0.005	7.34e-09	BMI	Locke	No
rs205262	6	34671142	G	A	0.273	0.022	0.004	1.75e-10	BMI	Locke	No

rs2033529	6	40456631	G	A	0.293	0.019	0.003	1.39e-08	BMI	Locke	Yes
rs2207139	6	50953449	G	A	0.177	0.045	0.004	4.13e-29	BMI	Locke	No
rs1167827	7	75001105	G	A	0.553	0.020	0.003	6.33e-10	BMI	Locke	No
rs2245368	7	76446079	C	T	0.180	0.032	0.006	3.19e-08	BMI	Locke	No
rs17405819	8	76969139	T	C	0.700	0.022	0.003	2.07e-11	BMI	Locke	No
rs2033732	8	85242264	C	T	0.747	0.019	0.004	4.89e-08	BMI	Locke	No
rs6477694	9	110972163	C	T	0.365	0.017	0.003	2.67e-08	BMI	Locke	No
rs1928295	9	119418304	T	C	0.548	0.019	0.003	7.91e-10	BMI	Locke	No
rs10733682	9	128500735	A	G	0.478	0.017	0.003	1.83e-08	BMI	Locke	No
rs4740619	9	15624326	T	C	0.542	0.018	0.003	4.56e-09	BMI	Locke	No
rs10968576	9	28404339	G	A	0.320	0.025	0.003	6.61e-14	BMI	Locke	No
rs17094222	10	102385430	C	T	0.211	0.025	0.004	5.94e-11	BMI	Locke	No
rs11191560	10	104859028	C	T	0.089	0.031	0.005	8.45e-09	BMI	Locke	Yes
rs7903146	10	114748339	C	T	0.713	0.023	0.003	1.11e-11	BMI	Locke	No
rs7899106	10	87400884	G	A	0.052	0.040	0.007	2.96e-08	BMI	Locke	No
rs12286929	11	114527614	G	A	0.523	0.022	0.003	1.31e-12	BMI	Locke	No

rs11030104	11	27641093	A	G	0.792	0.041	0.004	5.56e-28	BMI	Locke	No
rs2176598	11	43820854	T	C	0.251	0.020	0.004	2.97e-08	BMI	Locke	No
rs3817334	11	47607569	T	C	0.407	0.026	0.003	5.15e-17	BMI	Locke	No
rs4256980	11	8630515	G	C	0.646	0.021	0.003	2.9e-11	BMI	Locke	No
rs11057405	12	121347850	G	A	0.901	0.031	0.006	2.02e-08	BMI	Locke	No
rs7138803	12	48533735	A	G	0.384	0.032	0.003	8.15e-24	BMI	Locke	No
rs12016871	13	26915782	T	C	0.203	0.030	0.005	2.29e-10	BMI	Locke	Yes
rs12429545	13	53000207	A	G	0.133	0.033	0.005	1.09e-12	BMI	Locke	No
rs10132280	14	24998019	C	A	0.682	0.023	0.003	1.14e-11	BMI	Locke	No
rs12885454	14	28806589	C	A	0.642	0.021	0.003	1.94e-10	BMI	Locke	Yes
rs11847697	14	29584863	T	C	0.042	0.049	0.008	3.99e-09	BMI	Locke	Yes
rs7141420	14	78969207	T	C	0.527	0.024	0.003	1.23e-14	BMI	Locke	No
rs3736485	15	49535902	A	G	0.454	0.018	0.003	7.41e-09	BMI	Locke	No
rs16951275	15	65864222	T	C	0.784	0.031	0.004	1.91e-17	BMI	Locke	No
rs12446632	16	19842890	G	A	0.865	0.040	0.005	1.48e-18	BMI	Locke	No
rs2650492	16	28240912	A	G	0.303	0.021	0.004	1.92e-09	BMI	Locke	No
rs3888190	16	28796987	A	C	0.403	0.031	0.003	3.14e-23	BMI	Locke	Yes

rs9925964	16	31037396	A	G	0.620	0.019	0.003	8.11e-10	BMI	Locke		Yes
rs758747	16	3567359	T	C	0.265	0.023	0.004	7.47e-10	BMI	Locke		No
rs1558902	16	52361075	A	T	0.415	0.082	0.003	7.51e-153	BMI	Locke		No
rs1000940	17	5223976	G	A	0.320	0.019	0.003	1.28e-08	BMI	Locke		No
rs12940622	17	76230166	G	A	0.575	0.018	0.003	2.49e-09	BMI	Locke		No
rs1808579	18	19358886	C	T	0.534	0.017	0.003	4.17e-08	BMI	Locke		No
rs7243357	18	55034299	T	G	0.812	0.022	0.004	3.86e-08	BMI	Locke		No
rs6567160	18	55980115	C	T	0.236	0.056	0.004	3.93e-53	BMI	Locke		Yes
rs17724992	19	18315825	A	G	0.746	0.019	0.004	3.42e-08	BMI	Locke		No
rs29941	19	39001372	G	A	0.669	0.018	0.003	2.41e-08	BMI	Locke		No
rs2075650	19	50087459	A	G	0.848	0.026	0.005	1.25e-08	BMI	Locke		No
rs2287019	19	50894012	C	T	0.804	0.036	0.004	4.59e-18	BMI	Locke		Yes
rs3810291	19	52260843	A	G	0.666	0.028	0.004	4.81e-15	BMI	Locke		Yes
rs1158103	1	101024370	A	G	0.556	-0.010	0.002	6.73011e-09	BMI	Yengo	COJO	Yes
rs1730859	1	107617707	A	G	0.658	-0.011	0.002	6.37045e-11	BMI	Yengo	COJO	No
rs12035149	1	107885018	C	G	0.777	-0.016	0.002	7.39364e-14	BMI	Yengo	COJO	Yes
rs17531363	1	107977075	A	C	0.697	0.013	0.002	1.81415e-10	BMI	Yengo	COJO	Yes

rs7550711	1	110082886	T	C	0.031	0.064	0.005	2.38951e-35	BMI	Yengo	COJO	No
rs3768486	1	110123971	A	G	0.824	-0.012	0.002	6.24605e-09	BMI	Yengo	COJO	Yes
rs12033257	1	112318484	A	G	0.616	0.013	0.002	2.31124e-13	BMI	Yengo	COJO	Yes
rs10779751	1	11284336	A	G	0.274	0.014	0.002	9.26946e-15	BMI	Yengo	COJO	Yes
rs12731372	1	118852975	T	C	0.232	0.012	0.002	1.71405e-10	BMI	Yengo	COJO	Yes
rs10923724	1	119546842	T	C	0.572	-0.011	0.002	1.13784e-12	BMI	Yengo	COJO	Yes
rs6587552	1	151018861	A	G	0.241	0.015	0.002	6.46444e-13	BMI	Yengo	COJO	No
rs905938	1	154991389	T	C	0.732	-0.016	0.002	1.86277e-15	BMI	Yengo	COJO	Yes
rs11577179	1	155983710	A	G	0.372	-0.013	0.002	2.04004e-12	BMI	Yengo	COJO	Yes
rs17448682	1	15966713	T	C	0.237	0.013	0.002	3.10028e-10	BMI	Yengo	COJO	Yes
rs10733051	1	167280354	A	G	0.520	0.010	0.002	1.68951e-09	BMI	Yengo	COJO	No
rs696606	1	16828640	A	G	0.524	0.012	0.002	1.55353e-10	BMI	Yengo	COJO	No
rs12044597	1	1708801	A	G	0.497	-0.013	0.002	4.97046e-15	BMI	Yengo	COJO	No
rs761423	1	17301672	T	C	0.550	0.012	0.002	6.90881e-13	BMI	Yengo	COJO	No
rs912768	1	173473713	C	G	0.402	0.042	0.004	4.31118e-32	BMI	Yengo	COJO	Yes
rs12039524	1	173549827	A	G	0.175	-0.049	0.005	3.62648e-26	BMI	Yengo	COJO	Yes

rs11803119	1	174002465	A	T	0.018	0.059	0.009	7.67801e-11	BMI	Yengo	COJO	No
rs6681627	1	174126742	A	C	0.152	-0.057	0.005	1.69514e-27	BMI	Yengo	COJO	Yes
rs12564992	1	174478100	A	G	0.886	-0.038	0.004	4.51994e-26	BMI	Yengo	COJO	Yes
rs6700816	1	174883994	A	T	0.968	0.033	0.005	2.4252e-10	BMI	Yengo	COJO	No
rs11590474	1	174972588	T	C	0.792	-0.036	0.004	8.69777e-23	BMI	Yengo	COJO	Yes
rs17302346	1	174983543	T	C	0.976	-0.041	0.007	4.17082e-09	BMI	Yengo	COJO	Yes
rs543874	1	177889480	A	G	0.805	-0.047	0.002	2.86043e-116	BMI	Yengo	COJO	Yes
rs10920678	1	190239907	A	G	0.429	0.016	0.002	1.35149e-19	BMI	Yengo	COJO	No
rs12041258	1	195047936	T	C	0.771	0.015	0.002	1.78277e-12	BMI	Yengo	COJO	No
rs3762396	1	19510394	A	G	0.385	0.011	0.002	8.56253e-09	BMI	Yengo	COJO	Yes
rs10754210	1	197012111	A	G	0.311	-0.012	0.002	5.43686e-12	BMI	Yengo	COJO	Yes
rs2820311	1	201841476	A	G	0.663	-0.018	0.002	1.03187e-15	BMI	Yengo	COJO	No
rs9077	1	202116238	A	G	0.330	-0.016	0.002	2.79645e-14	BMI	Yengo	COJO	Yes
rs823074	1	205774839	T	C	0.588	0.012	0.002	4.55219e-12	BMI	Yengo	COJO	No
rs17014375	1	209543560	T	G	0.865	-0.016	0.003	1.17921e-10	BMI	Yengo	COJO	Yes
rs11118308	1	219633869	A	G	0.530	0.010	0.002	3.34527e-10	BMI	Yengo	COJO	No
rs10915840	1	225668524	A	G	0.283	-0.013	0.002	1.07384e-10	BMI	Yengo	COJO	No

rs967605	1	23399932	T	C	0.833	-0.017	0.002	3.67663e-13	BMI	Yengo	COJO	Yes
rs2491864	1	242986063	A	G	0.215	0.013	0.002	3.45974e-10	BMI	Yengo	COJO	No
rs12042959	1	243533273	A	G	0.850	0.018	0.002	1.15518e-13	BMI	Yengo	COJO	No
rs3753549	1	243722892	T	C	0.856	-0.023	0.003	6.93267e-19	BMI	Yengo	COJO	Yes
rs7535528	1	2444414	A	G	0.374	-0.015	0.002	6.52211e-16	BMI	Yengo	COJO	No
rs785278	1	33307987	A	T	0.177	-0.015	0.002	1.70527e-10	BMI	Yengo	COJO	No
rs4653017	1	33776728	T	C	0.682	0.011	0.002	3.23466e-09	BMI	Yengo	COJO	Yes
rs9426003	1	34602870	A	G	0.295	-0.011	0.002	3.96435e-09	BMI	Yengo	COJO	No
rs11583122	1	38053458	T	C	0.079	0.017	0.003	9.13865e-09	BMI	Yengo	COJO	Yes
rs2282231	1	39569571	T	C	0.225	0.013	0.002	3.81569e-10	BMI	Yengo	COJO	Yes
rs346722	1	45620134	T	C	0.115	0.025	0.004	6.975e-11	BMI	Yengo	COJO	No
rs946526	1	46487168	T	C	0.043	-0.032	0.005	6.86037e-12	BMI	Yengo	COJO	Yes
rs2275426	1	46487552	A	G	0.434	0.016	0.002	1.57379e-15	BMI	Yengo	COJO	Yes
rs6700838	1	47700027	T	C	0.596	-0.019	0.002	1.65645e-25	BMI	Yengo	COJO	Yes
rs7531656	1	49828663	A	G	0.325	0.019	0.002	2.39351e-28	BMI	Yengo	COJO	No
rs2356865	1	50836334	T	C	0.295	-0.012	0.002	6.45053e-10	BMI	Yengo	COJO	Yes
rs2481665	1	62594677	T	C	0.559	0.015	0.002	4.15622e-20	BMI	Yengo	COJO	No

rs11208662	1	65987164	C	G	0.088	0.021	0.003	1.14484e-11	BMI	Yengo	COJO	Yes
rs6577584	1	6715390	T	G	0.654	-0.012	0.002	5.02794e-11	BMI	Yengo	COJO	No
rs7531118	1	72837239	T	C	0.460	-0.022	0.002	5.13402e-35	BMI	Yengo	COJO	No
rs2590942	1	72885281	T	G	0.816	0.021	0.002	7.885e-21	BMI	Yengo	COJO	Yes
rs12042908	1	74997762	A	G	0.436	0.017	0.002	3.0995e-25	BMI	Yengo	COJO	Yes
rs12035349	1	77557339	A	G	0.870	-0.020	0.003	2.57251e-12	BMI	Yengo	COJO	Yes
rs17391694	1	78623626	T	C	0.119	0.029	0.003	4.68845e-29	BMI	Yengo	COJO	Yes
rs2154297	1	80791708	T	C	0.712	-0.011	0.002	5.9483e-09	BMI	Yengo	COJO	Yes
rs284227	1	82379446	T	C	0.745	-0.015	0.002	1.32264e-15	BMI	Yengo	COJO	No
rs7556169	1	8741401	A	G	0.386	-0.012	0.002	5.83387e-11	BMI	Yengo	COJO	Yes
rs6690764	1	92976590	A	G	0.792	-0.015	0.002	2.56438e-12	BMI	Yengo	COJO	No
rs1973993	1	96943994	T	C	0.410	-0.020	0.002	4.17264e-30	BMI	Yengo	COJO	Yes
rs2030342	1	97388226	T	C	0.575	0.017	0.002	4.16517e-20	BMI	Yengo	COJO	No
rs4372296	1	98320492	A	C	0.771	-0.019	0.002	5.47516e-19	BMI	Yengo	COJO	Yes
rs4303732	2	100830040	T	C	0.603	0.014	0.002	7.99856e-14	BMI	Yengo	COJO	No
rs12615778	2	102436738	A	G	0.694	0.013	0.002	2.69567e-10	BMI	Yengo	COJO	No

rs10203277	2	103496700	A	G	0.132	0.020	0.003	1.2606e-09	BMI	Yengo	COJO	Yes
rs6711584	2	104421692	A	G	0.454	0.019	0.002	2.41674e-23	BMI	Yengo	COJO	Yes
rs1451533	2	105466005	A	G	0.273	0.014	0.002	4.77242e-13	BMI	Yengo	COJO	Yes
rs4676084	2	110010962	A	G	0.410	0.011	0.002	5.93234e-10	BMI	Yengo	COJO	Yes
rs902695	2	113955074	A	G	0.480	-0.014	0.002	1.29157e-13	BMI	Yengo	COJO	No
rs7607490	2	12851120	A	G	0.108	0.018	0.003	5.3537e-10	BMI	Yengo	COJO	No
rs17551974	2	142293146	A	C	0.178	-0.013	0.002	8.89459e-09	BMI	Yengo	COJO	No
rs2890652	2	142959931	T	C	0.824	-0.017	0.002	1.92328e-13	BMI	Yengo	COJO	Yes
rs6710871	2	143960593	A	G	0.142	0.016	0.002	1.28741e-10	BMI	Yengo	COJO	No
rs7560871	2	145616899	A	G	0.073	0.020	0.003	3.0275e-09	BMI	Yengo	COJO	Yes
rs453520	2	147907202	T	C	0.583	-0.015	0.002	3.13197e-19	BMI	Yengo	COJO	Yes
rs16828086	2	151198990	C	G	0.617	0.011	0.002	5.5293e-09	BMI	Yengo	COJO	Yes
rs7600699	2	156018263	C	G	0.842	-0.014	0.002	5.41031e-09	BMI	Yengo	COJO	No
rs6738445	2	172599615	T	C	0.284	-0.017	0.002	2.01785e-15	BMI	Yengo	COJO	No
rs10930641	2	175000711	A	G	0.591	-0.016	0.002	4.52919e-17	BMI	Yengo	COJO	No
rs9630985	2	181607676	A	C	0.324	-0.013	0.002	9.11766e-12	BMI	Yengo	COJO	Yes
rs993954	2	188325474	T	G	0.572	0.012	0.002	3.65594e-09	BMI	Yengo	COJO	No

rs919433	2	198166565	A	G	0.359	0.014	0.002	1.36018e-11	BMI	Yengo	COJO	Yes
rs10497807	2	198585087	C	G	0.520	-0.018	0.002	2.85849e-23	BMI	Yengo	COJO	No
rs12991989	2	199169278	C	G	0.519	0.011	0.002	1.60445e-09	BMI	Yengo	COJO	Yes
rs7564679	2	204012790	A	G	0.428	-0.012	0.002	3.91065e-13	BMI	Yengo	COJO	No
rs12694021	2	206084372	A	C	0.448	0.010	0.002	3.86947e-09	BMI	Yengo	COJO	No
rs972540	2	207244783	A	G	0.727	-0.012	0.002	1.36622e-10	BMI	Yengo	COJO	Yes
rs17203016	2	208255518	A	G	0.804	-0.012	0.002	2.70838e-09	BMI	Yengo	COJO	Yes
rs4673553	2	211608379	T	G	0.544	-0.013	0.002	5.83087e-14	BMI	Yengo	COJO	No
rs1437929	2	211983316	A	G	0.288	0.012	0.002	1.00417e-09	BMI	Yengo	COJO	Yes
rs7599312	2	213413231	A	G	0.265	-0.018	0.002	1.20182e-19	BMI	Yengo	COJO	Yes
rs7607369	2	219279097	A	G	0.439	0.011	0.002	7.68387e-12	BMI	Yengo	COJO	Yes
rs11889536	2	220163543	A	G	0.851	0.019	0.002	8.91843e-14	BMI	Yengo	COJO	Yes
rs12479233	2	228891702	A	T	0.487	-0.010	0.002	5.37657e-09	BMI	Yengo	COJO	No
rs10211055	2	229016917	T	C	0.654	-0.014	0.002	1.11732e-14	BMI	Yengo	COJO	Yes
rs6720868	2	230663576	T	C	0.329	0.014	0.002	8.60289e-15	BMI	Yengo	COJO	Yes
rs10182181	2	25150296	A	G	0.525	-0.028	0.002	2.25727e-52	BMI	Yengo	COJO	No
rs4372836	2	28973883	T	C	0.303	0.015	0.002	3.79944e-16	BMI	Yengo	COJO	Yes

rs6548221	2	295255	A	G	0.225	0.015	0.002	3.58192e-14	BMI	Yengo	COJO	No
rs17327461	2	35512183	T	C	0.450	0.012	0.002	2.64188e-13	BMI	Yengo	COJO	No
rs4670626	2	37046657	T	C	0.357	-0.012	0.002	6.59668e-11	BMI	Yengo	COJO	No
rs6713781	2	40291940	C	G	0.414	-0.011	0.002	9.01419e-09	BMI	Yengo	COJO	Yes
rs4639527	2	416815	A	G	0.699	-0.016	0.002	3.74363e-15	BMI	Yengo	COJO	Yes
rs17035438	2	46878616	A	G	0.094	0.019	0.003	1.56414e-09	BMI	Yengo	COJO	No
rs2724861	2	471514	A	G	0.564	-0.015	0.002	1.67394e-13	BMI	Yengo	COJO	Yes
rs7561278	2	48954905	T	C	0.786	0.016	0.002	5.87265e-14	BMI	Yengo	COJO	No
rs930295	2	50233352	A	C	0.158	0.017	0.002	5.46874e-12	BMI	Yengo	COJO	Yes
rs7598402	2	50735943	C	G	0.510	0.015	0.002	2.95407e-15	BMI	Yengo	COJO	No
rs2194385	2	50865334	A	C	0.479	0.010	0.002	4.47905e-09	BMI	Yengo	COJO	Yes
rs968972	2	51171962	A	G	0.641	0.011	0.002	2.81091e-09	BMI	Yengo	COJO	Yes
rs7425440	2	512490	T	C	0.194	0.021	0.003	3.86968e-17	BMI	Yengo	COJO	Yes
rs2974255	2	516696	A	G	0.228	0.024	0.003	5.33271e-20	BMI	Yengo	COJO	No
rs10168197	2	51834839	C	G	0.200	-0.014	0.002	1.23238e-10	BMI	Yengo	COJO	Yes
rs7601895	2	55281901	C	G	0.704	0.017	0.002	4.12187e-16	BMI	Yengo	COJO	Yes

rs13432055	2	56603985	T	C	0.714	-0.013	0.002	2.46734e-13	BMI	Yengo	COJO	Yes
rs3922853	2	5830599	A	C	0.173	0.014	0.002	8.96396e-10	BMI	Yengo	COJO	No
rs6753170	2	58481863	T	C	0.373	0.014	0.002	9.48473e-11	BMI	Yengo	COJO	Yes
rs929641	2	58792377	A	G	0.584	0.014	0.002	3.31245e-13	BMI	Yengo	COJO	Yes
rs4671328	2	58935282	T	G	0.447	0.018	0.002	4.93169e-19	BMI	Yengo	COJO	No
rs6545714	2	59307725	A	G	0.614	-0.020	0.002	6.68067e-31	BMI	Yengo	COJO	No
rs4671358	2	60164634	A	T	0.596	0.015	0.002	9.07716e-14	BMI	Yengo	COJO	No
rs980329	2	60285100	T	C	0.752	-0.017	0.002	3.83944e-16	BMI	Yengo	COJO	Yes
rs4854326	2	603088	A	G	0.713	0.020	0.002	1.76908e-21	BMI	Yengo	COJO	Yes
rs12713433	2	61307982	T	C	0.793	0.015	0.002	1.3977e-10	BMI	Yengo	COJO	Yes
rs10929925	2	6155557	A	C	0.430	-0.011	0.002	7.76113e-10	BMI	Yengo	COJO	Yes
rs10190332	2	61619267	T	G	0.613	0.013	0.002	1.09443e-09	BMI	Yengo	COJO	Yes
rs13417156	2	62848319	T	C	0.564	-0.013	0.002	8.33453e-15	BMI	Yengo	COJO	Yes
rs13021737	2	632348	A	G	0.168	-0.060	0.002	5.93123e-135	BMI	Yengo	COJO	Yes
rs2902021	2	67825685	T	C	0.194	0.023	0.004	6.53027e-11	BMI	Yengo	COJO	Yes
rs7607351	2	69562127	T	C	0.581	0.012	0.002	1.23705e-12	BMI	Yengo	COJO	No
rs934515	2	79482643	A	G	0.118	0.018	0.003	7.45766e-11	BMI	Yengo	COJO	Yes

rs984902	2	81358877	A	T	0.884	0.019	0.003	5.05894e-11	BMI	Yengo	COJO	No
rs1371108	2	81816251	A	C	0.325	0.016	0.002	1.02212e-16	BMI	Yengo	COJO	Yes
rs7557796	2	86766153	T	C	0.348	0.018	0.002	1.65144e-21	BMI	Yengo	COJO	No
rs1436343	3	104606130	A	G	0.408	-0.012	0.002	2.35265e-12	BMI	Yengo	COJO	No
rs13321566	3	107342662	A	G	0.816	-0.015	0.002	3.09089e-11	BMI	Yengo	COJO	Yes
rs7640424	3	107820063	T	C	0.297	-0.012	0.002	1.39641e-11	BMI	Yengo	COJO	No
rs4273371	3	108119071	T	C	0.502	-0.011	0.002	2.23079e-11	BMI	Yengo	COJO	Yes
rs17681451	3	114399296	A	G	0.084	-0.027	0.003	4.13092e-15	BMI	Yengo	COJO	No
rs16823670	3	115071668	A	G	0.972	0.031	0.005	3.28303e-09	BMI	Yengo	COJO	Yes
rs3772934	3	115417865	T	C	0.283	0.011	0.002	7.56795e-09	BMI	Yengo	COJO	No
rs6804181	3	116937546	A	T	0.821	0.014	0.002	2.45937e-09	BMI	Yengo	COJO	Yes
rs4624596	3	119571541	T	C	0.815	0.014	0.002	2.08846e-09	BMI	Yengo	COJO	No
rs2124499	3	123093541	C	G	0.372	-0.013	0.002	1.30814e-13	BMI	Yengo	COJO	Yes
rs1899951	3	12394840	T	C	0.131	0.015	0.002	3.57934e-10	BMI	Yengo	COJO	No
rs1909586	3	124687767	T	G	0.598	-0.011	0.002	9.79232e-10	BMI	Yengo	COJO	Yes
rs9809534	3	125189782	C	G	0.877	0.016	0.003	3.62397e-10	BMI	Yengo	COJO	Yes
rs1320903	3	131758077	A	G	0.317	0.016	0.002	4.75739e-13	BMI	Yengo	COJO	No

rs580438	3	13345450	T	C	0.332	0.012	0.002	5.72335e-11	BMI	Yengo	COJO	Yes
rs10935143	3	134665159	A	G	0.454	-0.010	0.002	4.70963e-09	BMI	Yengo	COJO	No
rs9289499	3	135484734	T	C	0.896	0.026	0.003	1.12391e-14	BMI	Yengo	COJO	No
rs1014312	3	135621417	C	G	0.564	-0.023	0.002	2.91154e-21	BMI	Yengo	COJO	Yes
rs6786582	3	135898984	T	C	0.726	-0.070	0.004	1.81116e-57	BMI	Yengo	COJO	Yes
rs17199978	3	136056184	A	G	0.903	0.022	0.003	3.07136e-11	BMI	Yengo	COJO	Yes
rs181732	3	136744386	T	G	0.420	-0.030	0.003	1.0971e-26	BMI	Yengo	COJO	Yes
rs9881036	3	136845666	A	G	0.665	0.037	0.003	4.11005e-27	BMI	Yengo	COJO	Yes
rs4678297	3	136907111	T	C	0.300	0.024	0.003	7.11552e-19	BMI	Yengo	COJO	Yes
rs1600136	3	136979939	A	C	0.806	-0.032	0.003	1.90019e-27	BMI	Yengo	COJO	Yes
rs7616371	3	137047387	A	G	0.932	-0.021	0.004	9.3068e-09	BMI	Yengo	COJO	Yes
rs4342060	3	137215820	T	C	0.809	-0.020	0.003	1.08893e-14	BMI	Yengo	COJO	Yes
rs16851483	3	141275436	T	G	0.069	0.034	0.004	4.04561e-18	BMI	Yengo	COJO	Yes
rs355777	3	154034950	C	G	0.411	0.013	0.002	4.79917e-13	BMI	Yengo	COJO	No
rs7615297	3	156299313	C	G	0.854	0.014	0.002	3.67356e-09	BMI	Yengo	COJO	No
rs6767619	3	156893782	C	G	0.345	0.012	0.002	2.39553e-11	BMI	Yengo	COJO	Yes

rs827092	3	157985182	T	C	0.583	0.012	0.002	2.08538e-12	BMI	Yengo	COJO	Yes
rs11128760	3	15873407	A	G	0.403	0.011	0.002	4.99259e-11	BMI	Yengo	COJO	No
rs5396	3	170744815	T	C	0.724	-0.015	0.002	6.37272e-17	BMI	Yengo	COJO	No
rs13085472	3	171129859	T	C	0.348	0.011	0.002	1.28519e-09	BMI	Yengo	COJO	No
rs39654	3	173095123	A	G	0.445	-0.015	0.002	1.65693e-19	BMI	Yengo	COJO	Yes
rs1454148	3	176341188	T	C	0.267	0.012	0.002	1.63441e-09	BMI	Yengo	COJO	Yes
rs6443750	3	181329682	T	C	0.193	-0.013	0.002	4.88153e-10	BMI	Yengo	COJO	No
rs262956	3	183486117	T	G	0.347	0.011	0.002	8.32912e-09	BMI	Yengo	COJO	Yes
rs2293605	3	184044433	T	C	0.131	-0.016	0.003	3.74463e-09	BMI	Yengo	COJO	No
rs9816226	3	185834499	A	T	0.180	-0.023	0.003	2.08111e-18	BMI	Yengo	COJO	Yes
rs13072095	3	193639623	T	C	0.666	0.010	0.002	1.96427e-09	BMI	Yengo	COJO	Yes
rs6764533	3	196088464	A	G	0.359	0.011	0.002	9.61267e-10	BMI	Yengo	COJO	No
rs4858193	3	20441050	T	C	0.722	0.012	0.002	6.70792e-11	BMI	Yengo	COJO	Yes
rs11711337	3	21794904	A	T	0.716	-0.012	0.002	1.28816e-09	BMI	Yengo	COJO	Yes
rs6804842	3	25106437	A	G	0.428	-0.016	0.002	1.38172e-17	BMI	Yengo	COJO	Yes
rs6786125	3	28727523	C	G	0.819	-0.016	0.002	1.58655e-11	BMI	Yengo	COJO	No
rs10865858	3	34700713	T	C	0.598	0.011	0.002	1.97465e-09	BMI	Yengo	COJO	No

rs2047632	3	37153431	C	G	0.973	-0.038	0.006	1.82514e-10	BMI	Yengo	COJO	Yes
rs9814633	3	41310470	A	G	0.343	0.013	0.002	1.44127e-12	BMI	Yengo	COJO	No
rs10460960	3	42308735	A	G	0.888	0.019	0.003	1.88582e-13	BMI	Yengo	COJO	Yes
rs28350	3	42418446	A	G	0.193	0.014	0.002	6.04346e-09	BMI	Yengo	COJO	Yes
rs6442021	3	46742019	T	C	0.396	-0.011	0.002	1.70829e-10	BMI	Yengo	COJO	Yes
rs6442101	3	48130893	T	C	0.682	-0.019	0.002	1.41149e-27	BMI	Yengo	COJO	No
rs3731544	3	48207997	A	C	0.071	0.035	0.003	4.91723e-26	BMI	Yengo	COJO	Yes
rs17080319	3	48732480	T	C	0.879	0.057	0.004	3.95153e-48	BMI	Yengo	COJO	Yes
rs9846123	3	49088112	T	C	0.354	0.049	0.004	8.80598e-38	BMI	Yengo	COJO	Yes
rs12637576	3	49237334	T	C	0.617	0.027	0.004	8.71884e-14	BMI	Yengo	COJO	Yes
rs2230929	3	49343175	A	G	0.169	0.047	0.003	6.05958e-44	BMI	Yengo	COJO	Yes
rs2230590	3	49936102	T	C	0.492	-0.056	0.002	1.5432e-132	BMI	Yengo	COJO	No
rs12631248	3	50080174	C	G	0.922	-0.046	0.004	3.23523e-36	BMI	Yengo	COJO	Yes
rs2236950	3	50420554	A	C	0.185	-0.019	0.003	1.81224e-12	BMI	Yengo	COJO	Yes
rs9838283	3	50820486	A	G	0.798	0.111	0.005	5.48561e-113	BMI	Yengo	COJO	Yes
rs9827072	3	51184893	A	G	0.124	0.101	0.005	8.40715e-76	BMI	Yengo	COJO	Yes
rs13095652	3	51243837	T	C	0.438	-0.013	0.002	1.38786e-10	BMI	Yengo	COJO	Yes

rs11929028	3	51754424	T	G	0.075	0.079	0.004	2.78876e-72	BMI	Yengo	COJO	Yes
rs3821841	3	52084040	T	C	0.080	-0.023	0.003	2.44214e-11	BMI	Yengo	COJO	Yes
rs2710323	3	52815905	T	C	0.520	-0.015	0.002	2.82095e-19	BMI	Yengo	COJO	Yes
rs2680648	3	53777176	T	C	0.765	0.014	0.002	3.5378e-12	BMI	Yengo	COJO	Yes
rs12488237	3	56114861	T	C	0.948	-0.023	0.004	9.85839e-11	BMI	Yengo	COJO	Yes
rs10510321	3	6009092	T	C	0.203	0.012	0.002	5.20013e-09	BMI	Yengo	COJO	No
rs2365389	3	61236462	T	C	0.414	-0.013	0.002	8.11163e-12	BMI	Yengo	COJO	No
rs1452075	3	62481063	T	C	0.728	0.014	0.002	4.12357e-15	BMI	Yengo	COJO	No
rs925018	3	62713143	C	G	0.676	-0.012	0.002	2.63008e-10	BMI	Yengo	COJO	No
rs11915371	3	70539559	A	C	0.796	-0.014	0.002	1.32088e-11	BMI	Yengo	COJO	Yes
rs775731	3	77624784	T	C	0.588	-0.011	0.002	3.05398e-10	BMI	Yengo	COJO	No
rs1554193	3	8138801	A	T	0.471	-0.010	0.002	9.13265e-10	BMI	Yengo	COJO	No
rs3849570	3	81792112	A	C	0.341	0.016	0.002	8.32846e-19	BMI	Yengo	COJO	Yes
rs10511093	3	83763541	T	C	0.074	-0.027	0.004	3.63274e-11	BMI	Yengo	COJO	No
rs1375561	3	85658230	T	C	0.654	0.013	0.002	4.41456e-11	BMI	Yengo	COJO	No
rs2122042	3	85866335	T	G	0.206	0.024	0.002	1.94863e-26	BMI	Yengo	COJO	Yes

rs12638746	3	89331055	A	G	0.342	-0.026	0.003	9.35796e-16	BMI	Yengo	COJO	No
rs9832305	3	89392778	T	C	0.720	-0.023	0.003	3.60983e-15	BMI	Yengo	COJO	Yes
rs6551410	3	89442305	A	T	0.419	-0.049	0.004	9.66028e-30	BMI	Yengo	COJO	Yes
rs6803870	3	89443784	T	C	0.159	-0.033	0.004	7.52807e-16	BMI	Yengo	COJO	Yes
rs9714342	3	90428286	T	C	0.423	-0.039	0.003	2.41336e-43	BMI	Yengo	COJO	Yes
rs1454687	3	94038085	C	G	0.477	0.020	0.002	8.66275e-31	BMI	Yengo	COJO	Yes
rs3915844	3	9514856	A	G	0.143	0.020	0.003	3.7488e-13	BMI	Yengo	COJO	Yes
rs2850969	4	102183594	T	C	0.857	-0.014	0.002	2.15693e-09	BMI	Yengo	COJO	No
rs7377083	4	102708997	A	C	0.436	0.016	0.002	6.36212e-18	BMI	Yengo	COJO	Yes
rs13107325	4	103188709	T	C	0.074	0.045	0.003	2.44104e-41	BMI	Yengo	COJO	Yes
rs6843738	4	103936001	A	G	0.329	-0.011	0.002	2.92733e-11	BMI	Yengo	COJO	Yes
rs7692088	4	10491040	C	G	0.524	0.010	0.002	6.30866e-09	BMI	Yengo	COJO	No
rs326889	4	112713436	T	C	0.393	-0.012	0.002	3.19835e-11	BMI	Yengo	COJO	No
rs7694732	4	115124089	A	G	0.562	0.011	0.002	8.14477e-11	BMI	Yengo	COJO	No
rs1403846	4	119101723	T	C	0.828	0.012	0.002	8.95801e-09	BMI	Yengo	COJO	Yes
rs4864201	4	130731284	T	C	0.353	0.013	0.002	8.90254e-14	BMI	Yengo	COJO	No
rs1296328	4	137083193	A	C	0.434	0.015	0.002	2.20797e-14	BMI	Yengo	COJO	No

rs769674	4	140881964	A	T	0.678	0.012	0.002	5.57075e-11	BMI	Yengo	COJO	Yes
rs331949	4	143663206	T	C	0.627	-0.012	0.002	8.52054e-12	BMI	Yengo	COJO	Yes
rs1455137	4	145986668	A	C	0.620	-0.011	0.002	1.04913e-09	BMI	Yengo	COJO	Yes
rs11736228	4	147376805	A	T	0.741	0.012	0.002	3.52789e-09	BMI	Yengo	COJO	No
rs6827083	4	153075491	A	G	0.569	-0.012	0.002	2.89977e-12	BMI	Yengo	COJO	No
rs13110266	4	162129844	A	G	0.406	-0.011	0.002	8.50216e-11	BMI	Yengo	COJO	No
rs17538472	4	163038241	T	C	0.191	0.013	0.002	5.2932e-09	BMI	Yengo	COJO	Yes
rs6818414	4	16600664	T	C	0.508	-0.011	0.002	8.72369e-10	BMI	Yengo	COJO	No
rs1522569	4	171632637	T	G	0.818	0.015	0.002	2.46303e-11	BMI	Yengo	COJO	No
rs7683836	4	180167906	A	G	0.540	-0.012	0.002	1.01749e-11	BMI	Yengo	COJO	No
rs1477887	4	18514827	A	G	0.457	-0.013	0.002	4.05705e-13	BMI	Yengo	COJO	Yes
rs1323068	4	20263058	A	G	0.321	-0.013	0.002	1.84355e-11	BMI	Yengo	COJO	Yes
rs9291467	4	25428296	T	C	0.462	0.013	0.002	8.04729e-14	BMI	Yengo	COJO	No
rs6448587	4	28561990	A	C	0.811	0.015	0.002	1.78041e-10	BMI	Yengo	COJO	No
rs1345148	4	30843533	T	C	0.603	-0.010	0.002	6.80948e-09	BMI	Yengo	COJO	Yes
rs1000096	4	38692835	T	C	0.380	-0.013	0.002	1.57349e-13	BMI	Yengo	COJO	No
rs1866510	4	44514468	T	C	0.350	-0.011	0.002	2.36775e-09	BMI	Yengo	COJO	Yes

rs10938397	4	45182527	A	G	0.568	-0.033	0.002	6.91577e-92	BMI	Yengo	COJO	Yes
rs2768950	4	49064487	A	G	0.251	0.012	0.002	1.02725e-09	BMI	Yengo	COJO	No
rs711347	4	52926216	A	T	0.749	-0.012	0.002	5.79403e-10	BMI	Yengo	COJO	Yes
rs1492767	4	55221467	T	C	0.496	0.010	0.002	1.68602e-09	BMI	Yengo	COJO	No
rs2192158	4	55505360	A	G	0.460	0.015	0.002	1.16868e-17	BMI	Yengo	COJO	Yes
rs925421	4	60253877	A	G	0.266	0.013	0.002	1.285e-10	BMI	Yengo	COJO	Yes
rs4524456	4	6492739	A	G	0.524	-0.011	0.002	2.76931e-09	BMI	Yengo	COJO	No
rs11945861	4	65700865	A	G	0.237	-0.014	0.002	1.00132e-12	BMI	Yengo	COJO	No
rs7674623	4	80794681	T	C	0.198	0.015	0.002	1.87648e-11	BMI	Yengo	COJO	No
rs4148155	4	89054667	A	G	0.887	0.019	0.003	8.78069e-13	BMI	Yengo	COJO	Yes
rs1903579	4	91253956	C	G	0.550	0.012	0.002	3.61041e-13	BMI	Yengo	COJO	No
rs7710595	5	106506697	A	C	0.534	0.011	0.002	3.73862e-11	BMI	Yengo	COJO	No
rs40067	5	107439012	A	G	0.171	-0.023	0.002	9.40935e-23	BMI	Yengo	COJO	Yes
rs6595205	5	119372533	C	G	0.470	0.012	0.002	8.91755e-13	BMI	Yengo	COJO	No
rs7711753	5	122733317	A	G	0.436	-0.014	0.002	6.25017e-19	BMI	Yengo	COJO	No
rs6877851	5	130356413	C	G	0.234	-0.013	0.002	1.90086e-10	BMI	Yengo	COJO	Yes

rs329124	5	133865452	A	G	0.577	0.013	0.002	8.98125e-15	BMI	Yengo	COJO	No
rs13163306	5	136571959	A	G	0.474	-0.011	0.002	1.93703e-09	BMI	Yengo	COJO	No
rs7716275	5	137631073	T	G	0.193	-0.015	0.002	2.63497e-12	BMI	Yengo	COJO	No
rs160401	5	138061341	T	C	0.695	0.021	0.003	5.94354e-13	BMI	Yengo	COJO	Yes
rs4643949	5	138372345	T	C	0.366	0.022	0.003	3.78776e-13	BMI	Yengo	COJO	Yes
rs13174863	5	139080745	A	G	0.845	-0.020	0.002	1.00538e-16	BMI	Yengo	COJO	Yes
rs3844598	5	140992235	A	G	0.479	-0.012	0.002	4.59289e-11	BMI	Yengo	COJO	Yes
rs254428	5	141777439	T	G	0.580	0.010	0.002	4.23431e-09	BMI	Yengo	COJO	Yes
rs2190788	5	144484261	T	G	0.311	0.018	0.002	3.30289e-19	BMI	Yengo	COJO	No
rs10066835	5	151254297	T	C	0.016	0.045	0.007	1.15733e-09	BMI	Yengo	COJO	Yes
rs12659802	5	152274478	A	G	0.705	0.015	0.002	1.30303e-13	BMI	Yengo	COJO	Yes
rs10035289	5	153095918	A	G	0.474	0.011	0.002	3.35657e-11	BMI	Yengo	COJO	Yes
rs7715256	5	153537893	T	G	0.578	-0.015	0.002	1.35853e-19	BMI	Yengo	COJO	Yes
rs1650586	5	157516393	T	G	0.098	0.018	0.003	7.32041e-10	BMI	Yengo	COJO	No
rs17056301	5	158271680	T	C	0.736	-0.017	0.002	6.45927e-16	BMI	Yengo	COJO	Yes
rs7727781	5	165185571	T	C	0.520	0.010	0.002	6.08372e-09	BMI	Yengo	COJO	No
rs17525725	5	167293652	A	G	0.454	-0.010	0.002	8.8175e-09	BMI	Yengo	COJO	No

rs248139	5	167352783	A	G	0.193	0.016	0.002	4.7024e-12	BMI	Yengo	COJO	Yes
rs1014194	5	168192944	A	C	0.643	0.011	0.002	1.69987e-09	BMI	Yengo	COJO	Yes
rs7730898	5	170459675	A	G	0.729	0.013	0.002	2.44196e-11	BMI	Yengo	COJO	No
rs4518345	5	27185904	A	G	0.284	-0.012	0.002	4.41056e-10	BMI	Yengo	COJO	No
rs7730004	5	43191033	T	C	0.669	0.012	0.002	1.03683e-09	BMI	Yengo	COJO	No
rs12189178	5	50914726	T	C	0.038	0.028	0.005	8.89697e-09	BMI	Yengo	COJO	Yes
rs6879326	5	59208302	T	C	0.495	-0.010	0.002	5.81238e-09	BMI	Yengo	COJO	No
rs6449531	5	60712212	A	G	0.354	-0.016	0.002	2.8146e-16	BMI	Yengo	COJO	No
rs6888159	5	63932234	C	G	0.683	0.014	0.002	2.72807e-14	BMI	Yengo	COJO	No
rs2367112	5	64168193	T	G	0.508	0.012	0.002	2.14924e-11	BMI	Yengo	COJO	Yes
rs25832	5	66175682	A	G	0.732	0.015	0.002	2.01567e-13	BMI	Yengo	COJO	Yes
rs2307111	5	75003678	T	C	0.604	0.022	0.002	4.97592e-36	BMI	Yengo	COJO	No
rs368863	5	77372852	T	C	0.239	-0.015	0.002	1.109e-11	BMI	Yengo	COJO	Yes
rs12514473	5	80818639	T	C	0.769	0.016	0.002	1.07201e-15	BMI	Yengo	COJO	No
rs17591778	5	86420392	A	G	0.233	0.015	0.002	5.26562e-11	BMI	Yengo	COJO	Yes
rs7702514	5	86727027	T	C	0.173	-0.124	0.006	2.64069e-93	BMI	Yengo	COJO	No
rs186543	5	86754835	C	G	0.565	-0.035	0.002	3.55129e-52	BMI	Yengo	COJO	Yes

rs17285919	5	86908920	T	C	0.126	0.120	0.006	3.63293e-79	BMI	Yengo	COJO	Yes
rs1423627	5	87125578	T	C	0.779	-0.064	0.004	1.67293e-65	BMI	Yengo	COJO	Yes
rs710355	5	87159003	C	G	0.055	-0.027	0.004	2.71475e-11	BMI	Yengo	COJO	Yes
rs7444298	5	87730027	A	G	0.754	0.124	0.005	4.47589e-136	BMI	Yengo	COJO	Yes
rs13175892	5	87866793	T	C	0.976	0.100	0.008	2.78614e-40	BMI	Yengo	COJO	Yes
rs4916661	5	87932809	T	G	0.362	-0.026	0.002	1.62813e-31	BMI	Yengo	COJO	Yes
rs2098618	5	87934851	A	T	0.071	0.050	0.004	2.34246e-32	BMI	Yengo	COJO	No
rs2304607	5	87988733	A	G	0.852	-0.049	0.003	3.9951e-68	BMI	Yengo	COJO	Yes
rs10037047	5	88219964	A	G	0.835	-0.045	0.003	4.14171e-51	BMI	Yengo	COJO	Yes
rs12655756	5	88858208	A	T	0.370	0.012	0.002	4.16195e-11	BMI	Yengo	COJO	Yes
rs159032	5	94206202	T	C	0.244	0.012	0.002	1.97812e-09	BMI	Yengo	COJO	No
rs6235	5	95728898	C	G	0.730	-0.014	0.002	1.85809e-12	BMI	Yengo	COJO	Yes
rs2611742	5	95856501	T	C	0.596	-0.019	0.002	1.71161e-19	BMI	Yengo	COJO	Yes
rs174415	5	95933162	A	T	0.525	0.013	0.002	2.52584e-09	BMI	Yengo	COJO	Yes
rs3822683	5	96080883	A	G	0.781	0.012	0.002	5.95355e-09	BMI	Yengo	COJO	Yes
rs6919443	6	104493098	A	G	0.416	-0.010	0.002	9.01862e-09	BMI	Yengo	COJO	No

rs156151	6	104799007	C	G	0.191	-0.015	0.002	1.29801e-11	BMI	Yengo	COJO	Yes
rs3800229	6	108996963	T	G	0.712	0.015	0.002	1.49461e-15	BMI	Yengo	COJO	No
rs2357760	6	120213880	A	G	0.675	0.011	0.002	3.51729e-09	BMI	Yengo	COJO	No
rs2228213	6	12124855	A	G	0.348	-0.014	0.002	1.82971e-16	BMI	Yengo	COJO	Yes
rs2875762	6	124925032	C	G	0.247	0.012	0.002	1.37145e-09	BMI	Yengo	COJO	No
rs13209968	6	126089285	C	G	0.518	0.012	0.002	3.2246e-12	BMI	Yengo	COJO	Yes
rs6569648	6	130349119	T	C	0.773	-0.013	0.002	4.44881e-11	BMI	Yengo	COJO	No
rs9367368	6	13189275	T	C	0.697	0.014	0.002	4.24618e-14	BMI	Yengo	COJO	Yes
rs2781668	6	131897278	T	C	0.161	0.019	0.002	9.74546e-17	BMI	Yengo	COJO	Yes
rs13201877	6	137675541	A	G	0.860	-0.015	0.002	1.83471e-09	BMI	Yengo	COJO	No
rs2185027	6	153381622	A	C	0.703	-0.013	0.002	2.6334e-13	BMI	Yengo	COJO	No
rs10499276	6	154309808	T	C	0.124	0.015	0.003	3.17383e-09	BMI	Yengo	COJO	Yes
rs487060	6	160774459	T	C	0.482	0.011	0.002	7.64135e-11	BMI	Yengo	COJO	Yes
rs13191362	6	163033350	A	G	0.880	0.021	0.003	6.90641e-15	BMI	Yengo	COJO	Yes
rs2842385	6	19078274	A	G	0.802	-0.015	0.002	1.24269e-11	BMI	Yengo	COJO	Yes
rs9460306	6	19211776	T	C	0.091	0.019	0.003	1.3434e-09	BMI	Yengo	COJO	Yes
rs11753081	6	20705590	T	G	0.825	0.013	0.002	1.75755e-09	BMI	Yengo	COJO	No

rs7760082	6	21919387	A	G	0.665	-0.012	0.002	4.10241e-12	BMI	Yengo	COJO	No
rs6900723	6	23876240	T	C	0.676	-0.012	0.002	2.13029e-11	BMI	Yengo	COJO	Yes
rs13207082	6	27251379	A	G	0.916	-0.101	0.006	1.26755e-61	BMI	Yengo	COJO	Yes
rs17739298	6	27293049	C	G	0.895	0.035	0.003	3.42373e-27	BMI	Yengo	COJO	Yes
rs760880	6	27408181	T	G	0.636	0.033	0.003	1.21386e-36	BMI	Yengo	COJO	Yes
rs6908295	6	27527205	A	C	0.798	-0.022	0.003	1.70283e-15	BMI	Yengo	COJO	Yes
rs200968	6	27859568	T	C	0.836	0.079	0.005	5.6819e-56	BMI	Yengo	COJO	Yes
rs3734572	6	28059458	T	C	0.954	-0.031	0.004	4.82919e-13	BMI	Yengo	COJO	Yes
rs853679	6	28296863	A	C	0.141	0.073	0.004	1.58884e-67	BMI	Yengo	COJO	Yes
rs3819299	6	31322367	T	G	0.907	0.021	0.004	1.41251e-09	BMI	Yengo	COJO	No
rs498240	6	31892592	A	G	0.066	-0.025	0.004	2.87038e-12	BMI	Yengo	COJO	Yes
rs419261	6	33554147	T	C	0.404	0.010	0.002	9.26973e-09	BMI	Yengo	COJO	No
rs2814992	6	34617144	A	G	0.660	-0.052	0.003	1.08203e-60	BMI	Yengo	COJO	Yes
rs12215331	6	34644749	T	C	0.786	0.021	0.002	7.30549e-19	BMI	Yengo	COJO	Yes
rs6938239	6	34683635	A	G	0.850	0.029	0.004	2.52024e-14	BMI	Yengo	COJO	Yes
rs2140418	6	34975415	T	C	0.200	-0.043	0.003	2.46148e-36	BMI	Yengo	COJO	Yes
rs820077	6	35033854	A	G	0.809	0.028	0.003	1.49931e-22	BMI	Yengo	COJO	Yes

rs3807049	6	35512955	T	C	0.274	0.040	0.003	7.27987e-33	BMI	Yengo	COJO	Yes
rs17542466	6	35614744	A	G	0.772	-0.040	0.004	6.90303e-28	BMI	Yengo	COJO	Yes
rs1475774	6	35619554	A	G	0.023	0.075	0.007	2.60949e-24	BMI	Yengo	COJO	No
rs9394312	6	35672330	C	G	0.492	0.048	0.003	1.16582e-46	BMI	Yengo	COJO	Yes
rs9470086	6	35709678	A	C	0.017	0.072	0.008	7.16141e-21	BMI	Yengo	COJO	Yes
rs17757975	6	38214150	T	C	0.852	0.016	0.002	1.13249e-10	BMI	Yengo	COJO	Yes
rs847747	6	40080069	T	G	0.296	-0.011	0.002	8.45555e-09	BMI	Yengo	COJO	No
rs2033529	6	40348653	A	G	0.706	-0.015	0.002	5.62871e-11	BMI	Yengo	COJO	Yes
rs7748777	6	41133806	A	G	0.459	0.009	0.002	6.55803e-09	BMI	Yengo	COJO	Yes
rs9349239	6	42676480	A	G	0.492	0.011	0.002	2.84549e-09	BMI	Yengo	COJO	Yes
rs998584	6	43757896	A	C	0.478	-0.016	0.002	1.1514e-17	BMI	Yengo	COJO	Yes
rs13203286	6	49837540	T	G	0.060	0.033	0.004	8.71116e-15	BMI	Yengo	COJO	No
rs11756653	6	50054296	C	G	0.907	-0.023	0.004	3.86796e-09	BMI	Yengo	COJO	Yes
rs2295896	6	50566383	A	G	0.760	-0.015	0.003	3.21982e-09	BMI	Yengo	COJO	Yes
rs4383818	6	50756951	T	G	0.795	0.025	0.004	1.0285e-10	BMI	Yengo	COJO	Yes
rs10456637	6	50763935	A	T	0.741	0.043	0.004	1.76131e-26	BMI	Yengo	COJO	Yes

rs987237	6	50803050	A	G	0.820	-0.039	0.003	4.86229e-48	BMI	Yengo	COJO	No
rs2635727	6	50820940	T	C	0.254	-0.051	0.003	2.32227e-50	BMI	Yengo	COJO	Yes
rs1178060	6	50914343	A	G	0.847	-0.105	0.007	7.04604e-58	BMI	Yengo	COJO	Yes
rs2252300	6	51096424	A	T	0.208	0.022	0.003	3.91738e-17	BMI	Yengo	COJO	Yes
rs2504674	6	51160682	C	G	0.434	-0.015	0.002	5.41243e-15	BMI	Yengo	COJO	Yes
rs9370042	6	51546123	C	G	0.122	-0.018	0.003	2.96648e-10	BMI	Yengo	COJO	Yes
rs2397061	6	51638877	T	C	0.885	-0.039	0.004	6.28309e-25	BMI	Yengo	COJO	Yes
rs1266922	6	51822297	A	G	0.688	-0.016	0.002	8.43969e-12	BMI	Yengo	COJO	Yes
rs1358808	6	51825285	C	G	0.674	-0.030	0.002	2.6628e-43	BMI	Yengo	COJO	Yes
rs6922855	6	51843542	A	G	0.532	0.020	0.002	2.64808e-16	BMI	Yengo	COJO	Yes
rs765332	6	51874745	T	G	0.889	-0.025	0.003	8.25411e-14	BMI	Yengo	COJO	Yes
rs4278019	6	53693410	A	T	0.282	0.011	0.002	6.9883e-09	BMI	Yengo	COJO	Yes
rs816364	6	53990465	A	G	0.639	-0.011	0.002	4.43625e-09	BMI	Yengo	COJO	Yes
rs1503139	6	54724405	A	G	0.346	-0.013	0.002	6.93204e-11	BMI	Yengo	COJO	Yes
rs9475173	6	55013291	A	G	0.654	0.012	0.002	3.40892e-09	BMI	Yengo	COJO	Yes
rs2653365	6	55169801	T	C	0.832	-0.018	0.003	4.67401e-10	BMI	Yengo	COJO	Yes
rs1020548	6	56810539	A	G	0.834	-0.015	0.002	7.44533e-11	BMI	Yengo	COJO	Yes

rs12207241	6	57642076	A	G	0.617	-0.041	0.004	4.72933e-29	BMI	Yengo	COJO	No
rs4339513	6	57964315	T	C	0.903	0.045	0.005	2.0127e-18	BMI	Yengo	COJO	Yes
rs6459326	6	58060143	C	G	0.173	-0.022	0.004	8.8869e-09	BMI	Yengo	COJO	Yes
rs926279	6	58298846	A	G	0.709	0.031	0.004	5.04819e-17	BMI	Yengo	COJO	Yes
rs6904676	6	58705746	A	C	0.201	0.047	0.004	3.936e-27	BMI	Yengo	COJO	Yes
rs6922214	6	69968484	A	G	0.843	-0.015	0.002	1.62565e-09	BMI	Yengo	COJO	No
rs6921533	6	73742334	T	C	0.288	0.013	0.002	3.08638e-11	BMI	Yengo	COJO	Yes
rs9688431	6	73922654	T	C	0.940	0.022	0.004	2.46895e-10	BMI	Yengo	COJO	No
rs9294260	6	83433228	A	G	0.473	0.013	0.002	9.09341e-15	BMI	Yengo	COJO	No
rs13209753	6	86354442	A	G	0.939	-0.022	0.004	1.53979e-09	BMI	Yengo	COJO	Yes
rs1853639	6	87606842	A	G	0.636	-0.012	0.002	2.74369e-11	BMI	Yengo	COJO	Yes
rs9362662	6	90296588	A	G	0.480	0.011	0.002	1.84606e-09	BMI	Yengo	COJO	No
rs1324110	6	93913200	C	G	0.439	-0.011	0.002	7.31446e-11	BMI	Yengo	COJO	No
rs9463175	6	9510030	T	C	0.348	-0.012	0.002	1.59056e-11	BMI	Yengo	COJO	No
rs13203153	6	97374850	A	G	0.186	-0.016	0.002	5.70921e-12	BMI	Yengo	COJO	Yes
rs13209872	6	97753223	C	G	0.340	-0.013	0.002	6.23881e-12	BMI	Yengo	COJO	Yes
rs901630	6	98539519	T	C	0.397	-0.010	0.002	7.05009e-09	BMI	Yengo	COJO	No

rs9396763	6	9952059	A	C	0.220	0.013	0.002	9.86422e-09	BMI	Yengo	COJO	No
rs1048365	7	100804430	T	C	0.155	0.014	0.003	9.45386e-09	BMI	Yengo	COJO	Yes
rs11496125	7	103417557	T	C	0.421	0.015	0.002	4.48156e-16	BMI	Yengo	COJO	No
rs10953620	7	109173373	A	C	0.517	-0.010	0.002	6.55457e-09	BMI	Yengo	COJO	Yes
rs13227658	7	113353254	T	C	0.553	-0.021	0.002	7.07238e-29	BMI	Yengo	COJO	Yes
rs12705987	7	114349212	A	T	0.404	0.021	0.002	3.23798e-21	BMI	Yengo	COJO	No
rs1899689	7	121964349	T	C	0.399	0.012	0.002	6.1369e-14	BMI	Yengo	COJO	No
rs2283093	7	126721231	T	C	0.207	0.013	0.002	3.46607e-09	BMI	Yengo	COJO	No
rs10275044	7	1273845	A	T	0.208	-0.014	0.002	1.6653e-09	BMI	Yengo	COJO	Yes
rs7779498	7	130408415	T	C	0.039	-0.033	0.005	1.47218e-12	BMI	Yengo	COJO	Yes
rs972283	7	130466854	A	G	0.485	0.010	0.002	1.97133e-09	BMI	Yengo	COJO	Yes
rs1593304	7	131619847	A	G	0.199	0.013	0.002	7.61059e-09	BMI	Yengo	COJO	Yes
rs874454	7	131896813	A	G	0.338	-0.014	0.002	8.82457e-11	BMI	Yengo	COJO	Yes
rs3800649	7	137424509	A	G	0.277	0.011	0.002	7.078e-09	BMI	Yengo	COJO	No
rs1814170	7	138794149	A	T	0.895	0.021	0.003	1.05254e-12	BMI	Yengo	COJO	Yes
rs11773362	7	147668180	T	C	0.337	-0.011	0.002	6.00167e-10	BMI	Yengo	COJO	No

rs4725984	7	150668514	T	C	0.359	-0.012	0.002	6.73745e-13	BMI	Yengo	COJO	No
rs6968554	7	17287106	A	G	0.360	-0.010	0.002	3.8522e-09	BMI	Yengo	COJO	No
rs6461115	7	2103668	A	G	0.772	0.015	0.002	3.49808e-14	BMI	Yengo	COJO	No
rs40245	7	21470536	A	T	0.359	0.012	0.002	9.18926e-11	BMI	Yengo	COJO	Yes
rs4307239	7	24354300	A	G	0.542	-0.011	0.002	1.27589e-09	BMI	Yengo	COJO	Yes
rs12666574	7	26526960	A	G	0.650	0.013	0.002	2.24798e-12	BMI	Yengo	COJO	Yes
rs11971041	7	26698848	A	G	0.906	-0.019	0.003	1.35312e-09	BMI	Yengo	COJO	No
rs4722672	7	27231762	T	C	0.815	-0.013	0.002	2.55932e-09	BMI	Yengo	COJO	Yes
rs849135	7	28196413	A	G	0.491	0.012	0.002	4.21594e-13	BMI	Yengo	COJO	No
rs4722398	7	3125220	T	C	0.134	0.018	0.003	1.54732e-12	BMI	Yengo	COJO	Yes
rs215632	7	32368524	A	G	0.362	0.012	0.002	4.29754e-09	BMI	Yengo	COJO	Yes
rs329277	7	35080931	T	G	0.521	-0.010	0.002	6.33287e-09	BMI	Yengo	COJO	Yes
rs1229057	7	39054538	T	C	0.122	0.016	0.003	7.68433e-09	BMI	Yengo	COJO	No
rs10268050	7	44522617	T	C	0.795	-0.014	0.002	7.23031e-12	BMI	Yengo	COJO	No
rs799449	7	44784697	T	C	0.550	0.014	0.002	2.31498e-15	BMI	Yengo	COJO	No
rs10269783	7	49616203	A	G	0.390	0.014	0.002	7.33422e-16	BMI	Yengo	COJO	Yes
rs3807566	7	50564204	T	G	0.443	-0.012	0.002	2.33205e-12	BMI	Yengo	COJO	Yes

rs6463489	7	5542513	T	C	0.109	0.015	0.003	5.3148e-09	BMI	Yengo	COJO	No
rs7784465	7	6418275	T	C	0.861	-0.018	0.003	2.91861e-12	BMI	Yengo	COJO	Yes
rs1035010	7	69598328	T	C	0.257	0.014	0.002	4.68062e-12	BMI	Yengo	COJO	No
rs4718966	7	70040558	T	C	0.418	0.012	0.002	2.36696e-10	BMI	Yengo	COJO	Yes
rs993931	7	71888157	A	G	0.599	-0.011	0.002	2.78039e-09	BMI	Yengo	COJO	Yes
rs7777102	7	73058017	A	G	0.871	-0.014	0.002	8.35286e-09	BMI	Yengo	COJO	Yes
rs13227433	7	74094721	T	G	0.744	-0.015	0.002	2.33773e-12	BMI	Yengo	COJO	No
rs17207196	7	75101065	T	C	0.412	-0.018	0.002	3.03735e-20	BMI	Yengo	COJO	Yes
rs740157	7	77055885	A	G	0.432	0.011	0.002	4.37258e-11	BMI	Yengo	COJO	No
rs1544459	7	77417584	T	C	0.546	-0.010	0.002	1.33364e-10	BMI	Yengo	COJO	Yes
rs1852006	7	77829768	A	G	0.352	-0.013	0.002	2.77094e-10	BMI	Yengo	COJO	Yes
rs7805441	7	78121458	T	C	0.509	0.013	0.002	5.91291e-13	BMI	Yengo	COJO	Yes
rs6963840	7	78144371	T	C	0.211	0.016	0.002	3.37148e-11	BMI	Yengo	COJO	Yes
rs7796608	7	897847	A	G	0.827	0.015	0.003	2.71001e-09	BMI	Yengo	COJO	No
rs13247665	7	93232057	T	C	0.641	-0.012	0.002	9.27785e-11	BMI	Yengo	COJO	No
rs411717	7	94033031	T	C	0.440	-0.011	0.002	1.88515e-09	BMI	Yengo	COJO	No
rs13240600	7	99064466	A	G	0.845	0.022	0.002	2.48622e-18	BMI	Yengo	COJO	No

rs3134353	8	101947453	A	T	0.387	-0.012	0.002	3.31e-11	BMI	Yengo	COJO	No
rs12682565	8	10626280	A	G	0.037	0.034	0.005	3.36339e-13	BMI	Yengo	COJO	Yes
rs11250076	8	10647823	A	G	0.438	0.064	0.003	2.02654e-92	BMI	Yengo	COJO	Yes
rs7832003	8	10782004	C	G	0.180	-0.022	0.003	1.70984e-16	BMI	Yengo	COJO	Yes
rs11783247	8	10788875	T	C	0.538	-0.089	0.004	1.06703e-140	BMI	Yengo	COJO	Yes
rs9657542	8	10864363	C	G	0.364	0.102	0.004	9.32018e-172	BMI	Yengo	COJO	Yes
rs2409730	8	11060638	A	C	0.370	0.106	0.004	1.5156e-167	BMI	Yengo	COJO	Yes
rs12458	8	11617240	A	T	0.687	-0.025	0.002	1.07783e-33	BMI	Yengo	COJO	Yes
rs3808434	8	116559435	A	G	0.448	0.010	0.002	6.36224e-11	BMI	Yengo	COJO	No
rs2721965	8	116662038	A	C	0.666	0.014	0.002	2.50765e-14	BMI	Yengo	COJO	Yes
rs4841659	8	11828200	T	C	0.478	0.118	0.004	4.06441e-217	BMI	Yengo	COJO	Yes
rs11781699	8	118863061	T	C	0.810	-0.014	0.002	4.01987e-11	BMI	Yengo	COJO	No
rs10955841	8	118946541	A	G	0.669	0.014	0.002	7.50814e-14	BMI	Yengo	COJO	Yes
rs12675063	8	132879047	A	T	0.887	-0.016	0.003	1.75142e-09	BMI	Yengo	COJO	No
rs16906845	8	138215228	A	G	0.067	-0.023	0.004	1.13858e-09	BMI	Yengo	COJO	Yes
rs13263601	8	14095900	A	C	0.652	-0.012	0.002	5.13058e-11	BMI	Yengo	COJO	No

rs903959	8	142630782	A	T	0.396	0.011	0.002	2.73302e-09	BMI	Yengo	COJO	Yes
rs10110727	8	14324437	A	G	0.293	0.012	0.002	7.66696e-09	BMI	Yengo	COJO	Yes
rs4076358	8	144910239	A	G	0.621	0.010	0.002	1.56932e-09	BMI	Yengo	COJO	No
rs11987383	8	15197115	A	C	0.880	-0.016	0.003	1.40396e-09	BMI	Yengo	COJO	Yes
rs2543132	8	15536311	C	G	0.813	0.017	0.002	1.16975e-14	BMI	Yengo	COJO	Yes
rs4366093	8	20639811	T	C	0.320	-0.011	0.002	3.93907e-09	BMI	Yengo	COJO	No
rs11781222	8	23389571	T	C	0.871	0.015	0.002	1.18852e-10	BMI	Yengo	COJO	Yes
rs1594830	8	26334167	C	G	0.788	-0.012	0.002	3.82788e-09	BMI	Yengo	COJO	No
rs17446091	8	27167942	T	C	0.793	-0.012	0.002	3.90821e-09	BMI	Yengo	COJO	Yes
rs1982441	8	28021769	T	G	0.138	0.015	0.003	6.15557e-09	BMI	Yengo	COJO	Yes
rs2100814	8	28118130	A	G	0.410	0.012	0.002	3.19374e-11	BMI	Yengo	COJO	Yes
rs1362910	8	30856464	A	G	0.418	0.015	0.002	1.33528e-16	BMI	Yengo	COJO	Yes
rs7844647	8	34503776	T	C	0.732	0.013	0.002	3.38117e-12	BMI	Yengo	COJO	Yes
rs881301	8	38332318	T	C	0.582	-0.010	0.002	3.39391e-09	BMI	Yengo	COJO	No
rs17069831	8	4137396	T	C	0.280	-0.013	0.002	3.428e-10	BMI	Yengo	COJO	No
rs1658820	8	4288577	T	G	0.247	0.015	0.002	4.40724e-12	BMI	Yengo	COJO	No
rs4737183	8	64720693	A	G	0.530	0.012	0.002	4.41407e-11	BMI	Yengo	COJO	No

rs16932761	8	67202787	A	G	0.254	-0.014	0.002	4.62177e-12	BMI	Yengo	COJO	Yes
rs1431659	8	73439070	A	G	0.266	0.020	0.002	1.44305e-26	BMI	Yengo	COJO	Yes
rs2170382	8	74689288	T	C	0.120	0.017	0.003	5.13189e-10	BMI	Yengo	COJO	No
rs1405348	8	77228222	A	G	0.432	-0.013	0.002	6.66143e-12	BMI	Yengo	COJO	Yes
rs16907751	8	81375457	T	C	0.105	-0.020	0.003	3.83773e-11	BMI	Yengo	COJO	No
rs7827182	8	8380471	C	G	0.495	0.015	0.002	3.59448e-13	BMI	Yengo	COJO	No
rs733594	8	85077686	T	C	0.718	0.014	0.002	4.68855e-14	BMI	Yengo	COJO	Yes
rs2634047	8	85696337	C	G	0.242	-0.013	0.002	3.73667e-11	BMI	Yengo	COJO	No
rs7006629	8	87519542	T	C	0.526	0.012	0.002	2.31588e-12	BMI	Yengo	COJO	Yes
rs1700137	8	89461609	T	C	0.312	-0.013	0.002	2.13801e-12	BMI	Yengo	COJO	Yes
rs1394	8	9511654	A	G	0.640	-0.049	0.002	4.34438e-97	BMI	Yengo	COJO	Yes
rs12680842	8	95582606	A	G	0.680	0.011	0.002	3.46782e-10	BMI	Yengo	COJO	Yes
rs1399054	8	9785503	A	G	0.799	0.022	0.003	1.26318e-15	BMI	Yengo	COJO	Yes
rs497417	8	9790041	A	T	0.786	0.073	0.003	1.66596e-119	BMI	Yengo	COJO	Yes
rs450231	9	101481205	A	G	0.753	-0.014	0.002	2.58676e-12	BMI	Yengo	COJO	Yes
rs10118701	9	103061366	A	G	0.677	-0.013	0.002	3.46109e-12	BMI	Yengo	COJO	No
rs10989568	9	104396304	A	G	0.462	0.013	0.002	7.62983e-12	BMI	Yengo	COJO	Yes

rs7024334	9	109072075	T	G	0.226	0.012	0.002	9.14693e-10	BMI	Yengo	COJO	No
rs6477694	9	111932342	T	C	0.644	-0.012	0.002	4.57337e-12	BMI	Yengo	COJO	Yes
rs17820822	9	11831420	T	G	0.645	0.011	0.002	2.10335e-09	BMI	Yengo	COJO	No
rs1928295	9	120378483	T	C	0.554	0.015	0.002	2.09919e-20	BMI	Yengo	COJO	No
rs7865157	9	122631560	T	C	0.107	0.017	0.003	5.16415e-10	BMI	Yengo	COJO	Yes
rs10818810	9	126096522	A	G	0.391	0.011	0.002	1.16738e-09	BMI	Yengo	COJO	Yes
rs10818938	9	127049237	A	G	0.422	0.012	0.002	8.01125e-13	BMI	Yengo	COJO	Yes
rs4515655	9	128616073	T	C	0.401	-0.011	0.002	1.00576e-09	BMI	Yengo	COJO	Yes
rs3829849	9	129390800	T	C	0.359	0.012	0.002	7.83878e-12	BMI	Yengo	COJO	No
rs3902840	9	129419025	A	G	0.086	0.025	0.003	1.44143e-15	BMI	Yengo	COJO	Yes
rs13292976	9	129467340	T	C	0.446	0.011	0.002	1.74754e-09	BMI	Yengo	COJO	No
rs3739555	9	129940416	T	G	0.807	0.014	0.002	8.21748e-09	BMI	Yengo	COJO	Yes
rs7871866	9	131027982	C	G	0.153	0.015	0.003	2.76607e-09	BMI	Yengo	COJO	Yes
rs4740383	9	133783566	A	G	0.416	0.012	0.002	1.57894e-10	BMI	Yengo	COJO	Yes
rs11792069	9	140646121	A	G	0.830	0.015	0.002	3.75867e-10	BMI	Yengo	COJO	No
rs11790280	9	14651283	T	C	0.614	-0.011	0.002	2.61429e-09	BMI	Yengo	COJO	Yes

rs6474945	9	15670492	T	G	0.450	-0.017	0.002	2.14158e-25	BMI	Yengo	COJO	Yes
rs10962549	9	16719445	T	C	0.168	0.018	0.002	5.52433e-15	BMI	Yengo	COJO	Yes
rs483752	9	27612918	T	C	0.742	0.013	0.002	1.49735e-09	BMI	Yengo	COJO	No
rs7874154	9	27777012	T	C	0.502	-0.012	0.002	1.01335e-11	BMI	Yengo	COJO	Yes
rs1412235	9	28410996	C	G	0.318	0.033	0.002	2.42296e-52	BMI	Yengo	COJO	No
rs10971712	9	33820938	T	C	0.108	-0.018	0.003	7.28896e-11	BMI	Yengo	COJO	Yes
rs13290794	9	37183628	A	G	0.358	-0.013	0.002	3.14916e-12	BMI	Yengo	COJO	Yes
rs7042372	9	6959840	A	G	0.657	0.013	0.002	2.96483e-12	BMI	Yengo	COJO	No
rs2174307	9	73791849	C	G	0.407	0.011	0.002	3.16828e-11	BMI	Yengo	COJO	No
rs10867256	9	81367391	T	C	0.553	-0.011	0.002	7.00134e-11	BMI	Yengo	COJO	No
rs17351791	9	83263089	A	C	0.635	0.011	0.002	2.19507e-09	BMI	Yengo	COJO	No
rs1865341	9	8845911	T	C	0.758	0.013	0.002	1.00195e-10	BMI	Yengo	COJO	No
rs3739733	9	88897891	A	G	0.780	0.013	0.002	6.3254e-10	BMI	Yengo	COJO	Yes
rs10797115	9	92191256	T	C	0.536	0.012	0.002	3.35761e-12	BMI	Yengo	COJO	Yes
rs7869771	9	94180627	A	C	0.735	0.013	0.002	3.09775e-12	BMI	Yengo	COJO	No
rs4744275	9	96482633	A	G	0.266	0.011	0.002	1.46181e-09	BMI	Yengo	COJO	No
rs1983864	10	100017453	T	G	0.667	0.012	0.002	2.78521e-10	BMI	Yengo	COJO	No

rs17094222	10	102395440	T	C	0.796	-0.027	0.003	4.41621e-25	BMI	Yengo	COJO	Yes
rs11190661	10	102452136	T	C	0.315	-0.018	0.003	8.79762e-13	BMI	Yengo	COJO	Yes
rs10883553	10	102635475	A	C	0.451	0.012	0.002	1.66842e-10	BMI	Yengo	COJO	Yes
rs9787495	10	103206115	A	G	0.437	-0.011	0.002	5.00235e-09	BMI	Yengo	COJO	Yes
rs7083450	10	103984060	T	C	0.839	0.019	0.003	1.22652e-10	BMI	Yengo	COJO	Yes
rs10883759	10	104412049	A	G	0.302	-0.012	0.002	7.94294e-11	BMI	Yengo	COJO	Yes
rs12411886	10	104685299	A	C	0.083	0.034	0.003	1.14438e-26	BMI	Yengo	COJO	Yes
rs1712517	10	105033015	T	C	0.468	-0.012	0.002	3.32796e-10	BMI	Yengo	COJO	Yes
rs9419958	10	105675946	T	C	0.136	-0.015	0.003	5.52942e-09	BMI	Yengo	COJO	No
rs7903146	10	114758349	T	C	0.291	-0.013	0.002	5.16961e-11	BMI	Yengo	COJO	Yes
rs10886017	10	118672531	A	C	0.252	0.013	0.002	7.52007e-11	BMI	Yengo	COJO	No
rs845084	10	125220036	A	G	0.268	0.013	0.002	1.80689e-10	BMI	Yengo	COJO	No
rs17636031	10	126594078	T	C	0.730	-0.017	0.002	2.69494e-16	BMI	Yengo	COJO	No
rs7893571	10	16750129	T	G	0.662	0.014	0.002	4.06658e-14	BMI	Yengo	COJO	No
rs12776880	10	19776828	A	T	0.683	0.012	0.002	1.36018e-09	BMI	Yengo	COJO	No
rs7084454	10	21821274	A	G	0.335	0.020	0.002	1.04257e-25	BMI	Yengo	COJO	Yes
rs11251352	10	2585792	A	G	0.401	-0.012	0.002	1.98127e-10	BMI	Yengo	COJO	No

rs3781099	10	27318776	T	C	0.082	0.020	0.003	8.07102e-11	BMI	Yengo	COJO	Yes
rs3851083	10	33862727	A	G	0.432	-0.009	0.002	9.46767e-09	BMI	Yengo	COJO	No
rs1937684	10	53680085	A	T	0.659	0.011	0.002	6.09023e-10	BMI	Yengo	COJO	No
rs2163188	10	65314711	C	G	0.474	0.011	0.002	2.73381e-09	BMI	Yengo	COJO	No
rs12098284	10	76047464	T	C	0.124	0.016	0.003	6.06171e-09	BMI	Yengo	COJO	No
rs7899106	10	87410904	A	G	0.952	-0.032	0.004	1.67386e-17	BMI	Yengo	COJO	No
rs10887578	10	88096047	C	G	0.490	0.012	0.002	3.57876e-13	BMI	Yengo	COJO	No
rs2631681	10	93032943	T	C	0.325	-0.011	0.002	4.68066e-10	BMI	Yengo	COJO	Yes
rs793520	10	99032375	A	G	0.323	0.012	0.002	1.48511e-10	BMI	Yengo	COJO	No
rs577525	10	99769388	T	C	0.432	-0.013	0.002	1.15667e-13	BMI	Yengo	COJO	Yes
rs719802	11	113234679	T	C	0.380	0.011	0.002	1.76889e-09	BMI	Yengo	COJO	No
rs1048932	11	115044850	A	C	0.416	-0.016	0.002	9.94686e-21	BMI	Yengo	COJO	No
rs12417072	11	115623272	A	G	0.885	-0.016	0.003	2.42758e-09	BMI	Yengo	COJO	Yes
rs12420725	11	117017530	A	G	0.941	-0.022	0.004	6.31084e-09	BMI	Yengo	COJO	Yes
rs573455	11	117267884	A	G	0.453	-0.012	0.002	3.57389e-12	BMI	Yengo	COJO	Yes
rs1037587	11	11796727	T	C	0.454	0.010	0.002	7.2289e-09	BMI	Yengo	COJO	No

rs9332817	11	118365210	C	G	0.026	-0.035	0.006	8.71066e-09	BMI	Yengo	COJO	Yes
rs1003081	11	118913993	T	C	0.450	0.010	0.002	3.31688e-10	BMI	Yengo	COJO	Yes
rs4936671	11	121942512	C	G	0.367	0.012	0.002	4.98216e-11	BMI	Yengo	COJO	Yes
rs7941030	11	122522375	T	C	0.614	-0.011	0.002	6.15278e-11	BMI	Yengo	COJO	No
rs3134438	11	122765667	A	C	0.286	0.012	0.002	2.19897e-10	BMI	Yengo	COJO	Yes
rs1625427	11	131957293	T	C	0.650	0.013	0.002	1.06399e-13	BMI	Yengo	COJO	Yes
rs4936175	11	132641959	T	C	0.556	-0.013	0.002	3.02945e-14	BMI	Yengo	COJO	No
rs900144	11	13294268	T	C	0.567	0.016	0.002	7.07905e-21	BMI	Yengo	COJO	No
rs329651	11	133767622	T	G	0.806	0.017	0.002	4.79101e-15	BMI	Yengo	COJO	No
rs3802924	11	133827733	A	C	0.800	0.014	0.002	9.10631e-10	BMI	Yengo	COJO	Yes
rs12364470	11	134601012	T	G	0.837	-0.017	0.002	1.32129e-14	BMI	Yengo	COJO	No
rs10832778	11	17394073	C	G	0.378	-0.011	0.002	2.79434e-11	BMI	Yengo	COJO	Yes
rs10840606	11	2234690	A	G	0.826	-0.017	0.002	8.65956e-13	BMI	Yengo	COJO	No
rs7124442	11	27677041	T	C	0.683	-0.021	0.002	2.66729e-30	BMI	Yengo	COJO	No
rs6265	11	27679916	T	C	0.195	-0.036	0.002	1.69864e-56	BMI	Yengo	COJO	Yes
rs11030385	11	28629115	A	G	0.395	-0.019	0.002	5.11122e-19	BMI	Yengo	COJO	No
rs7948120	11	28763321	T	C	0.260	-0.013	0.002	1.15932e-10	BMI	Yengo	COJO	Yes

rs1552717	11	29158495	A	T	0.865	0.018	0.003	2.0221e-11	BMI	Yengo	COJO	No
rs1782507	11	30243868	T	G	0.653	-0.013	0.002	2.36874e-10	BMI	Yengo	COJO	Yes
rs223051	11	32131303	T	C	0.676	0.011	0.002	9.15017e-09	BMI	Yengo	COJO	Yes
rs10838122	11	43551416	T	C	0.480	-0.010	0.002	3.95969e-09	BMI	Yengo	COJO	No
rs12577642	11	43728534	A	T	0.686	-0.022	0.002	1.26198e-32	BMI	Yengo	COJO	Yes
rs10769165	11	45706453	T	C	0.523	-0.011	0.002	1.75087e-09	BMI	Yengo	COJO	Yes
rs12574668	11	46422686	A	C	0.178	0.035	0.004	1.28526e-22	BMI	Yengo	COJO	Yes
rs17197116	11	46520302	T	C	0.914	0.035	0.005	5.1285e-13	BMI	Yengo	COJO	Yes
rs11039014	11	46895378	A	G	0.774	0.016	0.002	3.28216e-12	BMI	Yengo	COJO	Yes
rs7124681	11	47529947	A	C	0.413	0.041	0.002	2.61265e-87	BMI	Yengo	COJO	Yes
rs7131262	11	47836302	A	T	0.260	-0.022	0.002	1.84353e-24	BMI	Yengo	COJO	Yes
rs10838852	11	48286256	T	C	0.563	-0.088	0.004	1.47824e-86	BMI	Yengo	COJO	Yes
rs7478904	11	48630323	T	C	0.128	-0.052	0.004	4.11206e-33	BMI	Yengo	COJO	Yes
rs1473579	11	48901553	A	G	0.412	-0.086	0.005	4.33017e-75	BMI	Yengo	COJO	No
rs7120873	11	49459474	T	C	0.111	0.054	0.004	1.86902e-47	BMI	Yengo	COJO	Yes
rs7924371	11	49620595	T	C	0.557	-0.050	0.004	1.20276e-42	BMI	Yengo	COJO	Yes
rs10839472	11	49994823	T	C	0.766	0.040	0.003	1.38527e-47	BMI	Yengo	COJO	Yes

rs2612203	11	54914689	A	G	0.035	0.040	0.005	2.38464e-13	BMI	Yengo	COJO	Yes
rs10459012	11	55091574	A	C	0.224	0.028	0.003	4.37001e-28	BMI	Yengo	COJO	No
rs551137	11	55323307	T	C	0.256	0.060	0.005	1.17603e-32	BMI	Yengo	COJO	Yes
rs11231548	11	55686588	A	G	0.987	-0.040	0.006	9.91979e-11	BMI	Yengo	COJO	Yes
rs4939051	11	56206141	C	G	0.789	0.066	0.006	1.38508e-30	BMI	Yengo	COJO	Yes
rs4542429	11	56446833	T	C	0.484	-0.029	0.003	1.07015e-24	BMI	Yengo	COJO	Yes
rs1943477	11	56973793	T	C	0.058	-0.022	0.004	3.72631e-10	BMI	Yengo	COJO	Yes
rs11600990	11	64082807	T	C	0.157	-0.015	0.002	8.14317e-10	BMI	Yengo	COJO	No
rs7102454	11	65594820	T	C	0.656	-0.012	0.002	4.14532e-11	BMI	Yengo	COJO	No
rs524281	11	65886662	A	C	0.758	-0.015	0.002	1.12088e-12	BMI	Yengo	COJO	Yes
rs7122539	11	66662731	A	G	0.342	-0.013	0.002	2.29158e-12	BMI	Yengo	COJO	No
rs587230	11	69299771	A	G	0.165	0.018	0.002	1.25498e-13	BMI	Yengo	COJO	Yes
rs1789165	11	69481969	A	G	0.639	0.013	0.002	4.99394e-13	BMI	Yengo	COJO	No
rs2440885	11	70563286	A	G	0.533	0.012	0.002	3.60716e-11	BMI	Yengo	COJO	Yes
rs7123876	11	72444583	T	C	0.754	-0.011	0.002	2.31532e-09	BMI	Yengo	COJO	Yes
rs7117238	11	78040259	A	G	0.168	-0.014	0.002	1.57471e-10	BMI	Yengo	COJO	Yes

rs1452134	11	86133416	T	C	0.542	-0.010	0.002	3.96532e-09	BMI	Yengo	COJO	No
rs12575252	11	8694073	C	G	0.351	-0.016	0.002	2.02836e-16	BMI	Yengo	COJO	Yes
rs10830452	11	89966202	A	G	0.671	-0.012	0.002	1.56737e-10	BMI	Yengo	COJO	Yes
rs2605603	11	93221105	A	G	0.489	-0.010	0.002	2.52753e-10	BMI	Yengo	COJO	No
rs4764949	12	103658096	A	G	0.664	0.019	0.002	2.27898e-24	BMI	Yengo	COJO	No
rs11611496	12	108413828	A	G	0.222	-0.015	0.002	1.14616e-13	BMI	Yengo	COJO	No
rs17608150	12	110046698	T	C	0.075	0.019	0.003	4.61594e-09	BMI	Yengo	COJO	Yes
rs6606686	12	110903380	C	G	0.690	-0.014	0.002	2.51573e-14	BMI	Yengo	COJO	Yes
rs6490055	12	111768973	A	G	0.767	-0.053	0.004	2.57023e-39	BMI	Yengo	COJO	Yes
rs1558236	12	111780998	C	G	0.973	0.056	0.007	9.85265e-15	BMI	Yengo	COJO	Yes
rs3809272	12	111800258	A	G	0.284	0.020	0.002	9.46305e-18	BMI	Yengo	COJO	Yes
rs12369009	12	112019799	T	G	0.797	0.061	0.005	3.44735e-34	BMI	Yengo	COJO	Yes
rs10850031	12	112771063	T	G	0.720	-0.045	0.004	2.1769e-28	BMI	Yengo	COJO	Yes
rs11066301	12	112871372	A	G	0.566	0.012	0.002	1.07391e-10	BMI	Yengo	COJO	Yes
rs4766710	12	114437708	A	G	0.936	0.023	0.004	1.36346e-10	BMI	Yengo	COJO	No
rs884282	12	117579274	T	C	0.575	-0.011	0.002	9.82197e-10	BMI	Yengo	COJO	No
rs7973955	12	118409640	A	G	0.285	-0.012	0.002	1.53119e-09	BMI	Yengo	COJO	Yes

rs3887080	12	121661966	A	G	0.121	0.018	0.003	4.40967e-11	BMI	Yengo	COJO	Yes
rs7133378	12	124409502	A	G	0.327	0.011	0.002	4.62226e-09	BMI	Yengo	COJO	Yes
rs10773049	12	124506631	T	C	0.598	-0.010	0.002	2.74118e-09	BMI	Yengo	COJO	No
rs7968230	12	133481917	A	G	0.323	0.012	0.002	4.70071e-11	BMI	Yengo	COJO	No
rs12422552	12	14413931	C	G	0.266	-0.014	0.002	1.78836e-12	BMI	Yengo	COJO	No
rs10744146	12	17212881	A	G	0.515	-0.014	0.002	5.93645e-15	BMI	Yengo	COJO	No
rs10840674	12	17360254	A	G	0.694	-0.011	0.002	1.69329e-09	BMI	Yengo	COJO	Yes
rs621042	12	18789007	A	C	0.451	-0.011	0.002	1.58072e-10	BMI	Yengo	COJO	Yes
rs7134375	12	20473758	A	C	0.434	0.012	0.002	4.55679e-10	BMI	Yengo	COJO	Yes
rs2429150	12	2152655	A	C	0.584	-0.012	0.002	8.05496e-12	BMI	Yengo	COJO	No
rs2467110	12	23067302	T	C	0.270	-0.014	0.002	1.3662e-10	BMI	Yengo	COJO	Yes
rs10842240	12	24060075	C	G	0.116	0.020	0.003	3.20943e-13	BMI	Yengo	COJO	Yes
rs10772055	12	33379440	C	G	0.866	-0.017	0.002	4.30356e-13	BMI	Yengo	COJO	No
rs12306932	12	38242029	T	C	0.510	-0.019	0.003	1.24124e-13	BMI	Yengo	COJO	Yes
rs17096549	12	38529333	A	G	0.976	0.053	0.006	3.73665e-17	BMI	Yengo	COJO	No
rs6580755	12	39159190	T	C	0.433	-0.033	0.004	1.49214e-17	BMI	Yengo	COJO	Yes
rs7958206	12	39329294	A	G	0.402	0.018	0.003	2.05433e-09	BMI	Yengo	COJO	Yes

rs10876418	12	39428802	T	C	0.232	-0.019	0.002	3.07576e-19	BMI	Yengo	COJO	Yes
rs11172702	12	39982413	A	G	0.923	0.032	0.004	1.34862e-16	BMI	Yengo	COJO	Yes
rs2733287	12	41880909	A	C	0.517	-0.016	0.002	5.39854e-21	BMI	Yengo	COJO	Yes
rs2240108	12	48180508	T	C	0.151	-0.016	0.003	1.8843e-09	BMI	Yengo	COJO	Yes
rs7965658	12	49987929	A	G	0.200	-0.014	0.002	9.96141e-10	BMI	Yengo	COJO	No
rs7138803	12	50247468	A	G	0.377	0.029	0.002	3.55981e-44	BMI	Yengo	COJO	Yes
rs4077093	12	51593616	T	G	0.217	0.013	0.002	4.28634e-09	BMI	Yengo	COJO	Yes
rs4759073	12	54653258	A	G	0.400	-0.012	0.002	1.18139e-11	BMI	Yengo	COJO	No
rs4759228	12	56508409	C	G	0.297	-0.014	0.002	3.78946e-14	BMI	Yengo	COJO	Yes
rs7975187	12	60964108	A	G	0.793	-0.014	0.002	7.78558e-11	BMI	Yengo	COJO	Yes
rs1819844	12	68205604	A	G	0.180	0.014	0.002	2.46482e-11	BMI	Yengo	COJO	No
rs10878946	12	69642315	T	C	0.714	-0.015	0.002	1.51006e-14	BMI	Yengo	COJO	Yes
rs11115176	12	82465797	T	C	0.760	0.017	0.002	7.05941e-15	BMI	Yengo	COJO	No
rs7313924	12	89899912	C	G	0.714	0.012	0.002	4.57627e-10	BMI	Yengo	COJO	No
rs2731222	12	90595383	A	C	0.270	0.012	0.002	4.00914e-10	BMI	Yengo	COJO	Yes
rs11611246	12	939480	T	G	0.210	0.025	0.002	6.92909e-35	BMI	Yengo	COJO	No

rs10745785	12	97586257	T	C	0.667	-0.011	0.002	9.00014e-10	BMI	Yengo	COJO	Yes
rs651548	12	99560183	A	G	0.368	0.013	0.002	3.34293e-10	BMI	Yengo	COJO	Yes
rs2479958	13	111984244	A	G	0.492	0.013	0.002	1.82522e-12	BMI	Yengo	COJO	No
rs1218822	13	28011963	A	G	0.666	0.015	0.002	2.1779e-18	BMI	Yengo	COJO	No
rs1006353	13	28047269	A	G	0.248	0.011	0.002	5.05348e-09	BMI	Yengo	COJO	Yes
rs9507983	13	28620036	T	C	0.607	-0.013	0.002	3.05857e-10	BMI	Yengo	COJO	Yes
rs9554263	13	28681228	C	G	0.769	-0.012	0.002	6.75789e-09	BMI	Yengo	COJO	Yes
rs1045411	13	31033232	T	C	0.265	-0.015	0.002	8.26436e-16	BMI	Yengo	COJO	No
rs9595908	13	33184288	T	C	0.628	0.016	0.002	1.81783e-20	BMI	Yengo	COJO	Yes
rs9544915	13	36230485	T	C	0.860	0.015	0.003	1.5256e-09	BMI	Yengo	COJO	Yes
rs9603697	13	40783323	T	C	0.319	0.015	0.002	2.98939e-16	BMI	Yengo	COJO	No
rs12429545	13	54102206	A	G	0.125	0.034	0.003	8.52812e-40	BMI	Yengo	COJO	No
rs10467530	13	54694130	C	G	0.136	0.019	0.003	2.58264e-12	BMI	Yengo	COJO	Yes
rs9527706	13	58402479	A	G	0.729	-0.011	0.002	9.75658e-09	BMI	Yengo	COJO	No
rs9538141	13	59178258	A	G	0.509	0.013	0.002	1.60147e-12	BMI	Yengo	COJO	Yes
rs1333423	13	59425111	A	T	0.225	0.015	0.002	2.40161e-11	BMI	Yengo	COJO	Yes
rs892261	13	65884191	T	C	0.443	-0.012	0.002	3.61498e-10	BMI	Yengo	COJO	Yes

rs9540493	13	66205704	A	G	0.442	0.017	0.002	3.24607e-21	BMI	Yengo	COJO	Yes
rs9571687	13	67472713	A	C	0.329	-0.017	0.002	4.09886e-19	BMI	Yengo	COJO	No
rs629443	13	76386075	T	G	0.250	0.011	0.002	5.33532e-09	BMI	Yengo	COJO	Yes
rs1668633	13	78371890	T	C	0.574	0.011	0.002	1.59002e-10	BMI	Yengo	COJO	No
rs9530843	13	79563749	A	C	0.556	0.014	0.002	3.98457e-14	BMI	Yengo	COJO	No
rs1927790	13	96922191	T	C	0.589	-0.013	0.002	2.15136e-14	BMI	Yengo	COJO	No
rs7334078	13	99120484	T	C	0.712	0.013	0.002	2.45311e-11	BMI	Yengo	COJO	No
rs12147845	14	101144596	T	C	0.114	0.020	0.003	2.17551e-13	BMI	Yengo	COJO	Yes
rs7147503	14	101539384	T	C	0.370	-0.012	0.002	9.74881e-12	BMI	Yengo	COJO	Yes
rs8016771	14	102649451	T	G	0.912	-0.022	0.003	4.3261e-12	BMI	Yengo	COJO	Yes
rs3803286	14	103246470	A	G	0.343	0.017	0.002	1.988e-20	BMI	Yengo	COJO	Yes
rs2010281	14	103862322	A	G	0.355	-0.011	0.002	8.42863e-09	BMI	Yengo	COJO	Yes
rs10132280	14	25928179	A	C	0.302	-0.020	0.002	2.25306e-27	BMI	Yengo	COJO	No
rs4981693	14	29680331	A	G	0.771	0.016	0.002	1.20011e-13	BMI	Yengo	COJO	No
rs12885454	14	29736838	A	C	0.343	-0.015	0.002	2.81474e-16	BMI	Yengo	COJO	Yes
rs8016859	14	30484722	C	G	0.040	0.033	0.004	2.48964e-14	BMI	Yengo	COJO	Yes
rs17522122	14	33302882	T	G	0.481	0.016	0.002	6.8271e-22	BMI	Yengo	COJO	Yes

rs9806058	14	35673470	A	T	0.877	0.015	0.003	9.67137e-09	BMI	Yengo	COJO	Yes
rs1956151	14	40101060	A	G	0.821	-0.016	0.002	6.21278e-12	BMI	Yengo	COJO	No
rs12587412	14	47272423	T	G	0.490	0.011	0.002	5.40259e-10	BMI	Yengo	COJO	Yes
rs217671	14	62360464	A	G	0.728	-0.013	0.002	4.57761e-11	BMI	Yengo	COJO	No
rs2412107	14	65426216	T	G	0.208	0.014	0.002	2.13314e-10	BMI	Yengo	COJO	Yes
rs11844682	14	65910844	C	G	0.661	-0.010	0.002	9.6839e-09	BMI	Yengo	COJO	Yes
rs3902951	14	69789755	T	G	0.754	-0.012	0.002	3.35658e-09	BMI	Yengo	COJO	No
rs1205106	14	72269668	A	G	0.542	-0.010	0.002	8.01841e-09	BMI	Yengo	COJO	Yes
rs17105272	14	77529783	T	C	0.319	0.011	0.002	2.22132e-09	BMI	Yengo	COJO	No
rs10146527	14	79499850	T	C	0.636	0.013	0.002	2.3724e-14	BMI	Yengo	COJO	Yes
rs2003616	14	79903993	T	G	0.288	0.013	0.002	9.02933e-10	BMI	Yengo	COJO	Yes
rs7144011	14	79940383	T	G	0.214	0.030	0.002	1.21977e-34	BMI	Yengo	COJO	Yes
rs799132	14	82684748	A	T	0.221	-0.012	0.002	5.68499e-09	BMI	Yengo	COJO	No
rs12888545	14	88308044	A	G	0.748	-0.017	0.002	3.76464e-16	BMI	Yengo	COJO	No
rs1951455	14	91512339	T	C	0.275	-0.014	0.002	8.93136e-13	BMI	Yengo	COJO	Yes
rs2160077	14	92428410	A	G	0.429	0.012	0.002	1.08738e-12	BMI	Yengo	COJO	Yes

rs10131890	14	97258752	A	C	0.950	-0.025	0.004	1.56419e-10	BMI	Yengo	COJO	No
rs17096552	14	98626578	A	G	0.136	-0.020	0.003	2.53438e-12	BMI	Yengo	COJO	No
rs3850422	14	99671788	A	G	0.446	-0.011	0.002	3.64218e-12	BMI	Yengo	COJO	Yes
rs4906908	15	27040082	T	G	0.475	-0.010	0.002	1.49701e-09	BMI	Yengo	COJO	No
rs4284600	15	31843528	T	C	0.529	-0.010	0.002	7.16318e-09	BMI	Yengo	COJO	No
rs7181610	15	35826859	A	T	0.858	0.015	0.003	4.16197e-09	BMI	Yengo	COJO	Yes
rs8036040	15	36402716	A	C	0.493	0.011	0.002	1.24255e-10	BMI	Yengo	COJO	No
rs316611	15	41751678	T	C	0.255	0.013	0.002	1.71752e-09	BMI	Yengo	COJO	Yes
rs12439798	15	46584787	T	G	0.423	0.013	0.002	3.56592e-14	BMI	Yengo	COJO	No
rs3736485	15	51748610	A	G	0.456	0.012	0.002	1.13907e-12	BMI	Yengo	COJO	Yes
rs1657930	15	57120989	A	G	0.803	-0.017	0.002	1.36983e-12	BMI	Yengo	COJO	No
rs340025	15	60908307	T	C	0.428	-0.012	0.002	9.83373e-13	BMI	Yengo	COJO	No
rs8033510	15	61445514	T	C	0.371	0.012	0.002	1.91955e-10	BMI	Yengo	COJO	Yes
rs17238110	15	62150364	A	G	0.837	0.035	0.005	2.0236e-12	BMI	Yengo	COJO	Yes
rs12595158	15	62316035	T	C	0.024	-0.040	0.005	1.54389e-13	BMI	Yengo	COJO	Yes
rs11635675	15	63793238	T	G	0.646	0.017	0.002	2.10913e-19	BMI	Yengo	COJO	No
rs6494481	15	64849904	T	G	0.119	0.022	0.003	1.12657e-11	BMI	Yengo	COJO	Yes

rs11629783	15	66741387	C	G	0.769	0.015	0.002	6.63492e-13	BMI	Yengo	COJO	Yes
rs16951319	15	68103632	T	C	0.134	-0.017	0.003	1.07389e-09	BMI	Yengo	COJO	Yes
rs13329567	15	68104367	T	C	0.231	-0.035	0.002	8.08292e-56	BMI	Yengo	COJO	Yes
rs7164727	15	73093991	T	C	0.681	0.017	0.002	2.23894e-24	BMI	Yengo	COJO	Yes
rs2593280	15	76150965	A	G	0.852	0.015	0.003	1.14475e-09	BMI	Yengo	COJO	No
rs403656	15	76755506	A	G	0.850	0.072	0.006	8.81617e-38	BMI	Yengo	COJO	Yes
rs2459359	15	76863838	C	G	0.948	0.066	0.006	1.99762e-27	BMI	Yengo	COJO	Yes
rs10519151	15	77156899	A	T	0.067	0.031	0.005	4.80962e-10	BMI	Yengo	COJO	Yes
rs4886506	15	77207277	T	G	0.695	0.040	0.004	6.68108e-24	BMI	Yengo	COJO	Yes
rs12148386	15	77254544	T	C	0.458	0.048	0.004	2.56438e-29	BMI	Yengo	COJO	Yes
rs4886869	15	77799657	A	G	0.395	-0.029	0.002	2.75464e-33	BMI	Yengo	COJO	No
rs8024932	15	77915282	T	G	0.893	0.021	0.003	3.42207e-12	BMI	Yengo	COJO	Yes
rs11855853	15	78012618	T	C	0.265	-0.021	0.002	9.91551e-23	BMI	Yengo	COJO	No
rs6495252	15	78117685	T	C	0.383	0.013	0.002	2.81001e-12	BMI	Yengo	COJO	Yes
rs12595749	15	79432359	A	G	0.571	0.015	0.002	1.4718e-18	BMI	Yengo	COJO	Yes
rs12593036	15	81058652	A	G	0.701	0.016	0.002	3.1853e-15	BMI	Yengo	COJO	Yes
rs12902742	15	83647483	A	T	0.091	0.021	0.003	9.51619e-11	BMI	Yengo	COJO	Yes

rs11259933	15	84580156	A	G	0.523	-0.013	0.002	1.67038e-12	BMI	Yengo	COJO	Yes
rs150353	15	89928189	T	G	0.556	-0.011	0.002	7.75046e-10	BMI	Yengo	COJO	No
rs12101393	15	92570921	C	G	0.780	0.016	0.002	8.18539e-12	BMI	Yengo	COJO	No
rs7181498	15	95271404	T	C	0.369	0.015	0.002	1.42444e-17	BMI	Yengo	COJO	Yes
rs4985155	16	15129459	A	G	0.663	0.012	0.002	1.03746e-10	BMI	Yengo	COJO	Yes
rs12446632	16	19935389	A	G	0.142	-0.034	0.002	1.05213e-42	BMI	Yengo	COJO	No
rs868554	16	20050466	C	G	0.754	-0.017	0.002	3.20942e-17	BMI	Yengo	COJO	Yes
rs11074446	16	20255123	T	C	0.869	0.025	0.002	6.90089e-25	BMI	Yengo	COJO	Yes
rs9931967	16	20375351	T	G	0.508	0.015	0.002	2.54903e-18	BMI	Yengo	COJO	Yes
rs2516739	16	2097158	A	G	0.217	-0.013	0.002	9.47971e-09	BMI	Yengo	COJO	No
rs9927848	16	23833071	A	C	0.733	-0.013	0.002	8.43217e-11	BMI	Yengo	COJO	No
rs7195386	16	24578458	T	C	0.501	0.015	0.002	4.46158e-18	BMI	Yengo	COJO	No
rs1862451	16	24803620	A	G	0.731	0.016	0.002	1.70606e-15	BMI	Yengo	COJO	Yes
rs7187776	16	28857645	A	G	0.593	-0.027	0.002	1.39499e-62	BMI	Yengo	COJO	Yes
rs1057452	16	29833714	A	G	0.037	0.017	0.002	1.32895e-12	BMI	Yengo	COJO	Yes
rs3814883	16	29994922	T	C	0.476	0.023	0.002	5.78877e-43	BMI	Yengo	COJO	No

rs1549293	16	31141993	T	C	0.360	-0.017	0.002	4.03338e-21	BMI	Yengo	COJO	Yes
rs12448257	16	3599655	A	G	0.218	0.022	0.002	6.10817e-26	BMI	Yengo	COJO	Yes
rs3794702	16	3730613	A	T	0.196	0.014	0.002	5.16233e-09	BMI	Yengo	COJO	No
rs11866815	16	387867	T	C	0.246	-0.017	0.002	6.4716e-19	BMI	Yengo	COJO	No
rs879620	16	4015729	T	C	0.618	0.016	0.002	2.05295e-11	BMI	Yengo	COJO	Yes
rs2080454	16	49062590	A	C	0.621	-0.011	0.002	7.26363e-10	BMI	Yengo	COJO	No
rs1564981	16	50986308	A	G	0.458	0.011	0.002	2.74368e-11	BMI	Yengo	COJO	Yes
rs17795934	16	51926509	T	C	0.298	-0.011	0.002	4.17013e-10	BMI	Yengo	COJO	No
rs12443621	16	52548037	A	G	0.533	-0.012	0.002	1.36229e-11	BMI	Yengo	COJO	Yes
rs16952479	16	53770578	A	T	0.946	-0.036	0.005	2.70518e-15	BMI	Yengo	COJO	Yes
rs8047395	16	53798523	A	G	0.506	0.041	0.004	8.20676e-30	BMI	Yengo	COJO	Yes
rs11075986	16	53805344	C	G	0.915	0.030	0.005	8.96878e-11	BMI	Yengo	COJO	Yes
rs3751813	16	53818708	T	G	0.541	0.018	0.003	4.32607e-12	BMI	Yengo	COJO	Yes
rs9931164	16	53825238	A	G	0.982	0.080	0.006	1.71441e-37	BMI	Yengo	COJO	Yes
rs9922708	16	53831146	T	C	0.432	0.031	0.003	4.65792e-21	BMI	Yengo	COJO	Yes
rs2075205	16	54153099	A	T	0.587	0.013	0.002	2.42771e-14	BMI	Yengo	COJO	No
rs907011	16	54234492	T	G	0.703	0.012	0.002	1.40447e-09	BMI	Yengo	COJO	Yes

rs12448738	16	56489343	A	C	0.863	-0.015	0.003	3.38416e-09	BMI	Yengo	COJO	Yes
rs11075489	16	62803841	T	C	0.483	-0.011	0.002	9.90863e-10	BMI	Yengo	COJO	No
rs2534760	16	6509009	A	T	0.706	-0.014	0.002	4.31855e-12	BMI	Yengo	COJO	No
rs10083803	16	6701400	T	C	0.260	-0.011	0.002	8.31941e-09	BMI	Yengo	COJO	Yes
rs9931407	16	67290155	T	C	0.967	0.046	0.006	4.69059e-15	BMI	Yengo	COJO	No
rs7200919	16	67316600	A	G	0.413	0.055	0.004	5.19837e-49	BMI	Yengo	COJO	Yes
rs12920590	16	67420603	T	C	0.648	0.038	0.003	1.10649e-31	BMI	Yengo	COJO	Yes
rs2863981	16	68295598	A	G	0.410	-0.041	0.004	9.52432e-32	BMI	Yengo	COJO	Yes
rs2307022	16	68381978	A	G	0.334	0.051	0.003	5.43277e-54	BMI	Yengo	COJO	Yes
rs10500548	16	69174141	T	C	0.058	0.022	0.004	2.35056e-09	BMI	Yengo	COJO	Yes
rs889398	16	69556715	T	C	0.425	-0.018	0.002	8.76066e-28	BMI	Yengo	COJO	Yes
rs7919	16	70514828	A	C	0.450	-0.012	0.002	1.17538e-11	BMI	Yengo	COJO	Yes
rs11642001	16	71899586	A	G	0.212	-0.025	0.003	8.69724e-16	BMI	Yengo	COJO	Yes
rs952159	16	71965915	A	G	0.335	0.018	0.003	1.24499e-11	BMI	Yengo	COJO	Yes
rs756717	16	72996162	A	G	0.397	-0.015	0.002	8.4282e-15	BMI	Yengo	COJO	Yes
rs825680	16	73606563	A	T	0.583	0.011	0.002	6.65292e-09	BMI	Yengo	COJO	Yes
rs6564360	16	76779612	A	G	0.810	-0.013	0.002	4.86168e-09	BMI	Yengo	COJO	No

rs8046061	16	80752293	T	C	0.550	0.010	0.002	3.82997e-09	BMI	Yengo	COJO	No
rs12922346	16	82438337	C	G	0.266	0.012	0.002	2.03531e-09	BMI	Yengo	COJO	Yes
rs4783241	16	82650384	C	G	0.494	-0.011	0.002	1.0154e-09	BMI	Yengo	COJO	Yes
rs7206608	16	82872628	C	G	0.685	-0.012	0.002	6.66401e-11	BMI	Yengo	COJO	Yes
rs977540	16	9724750	A	G	0.762	0.012	0.002	6.35598e-10	BMI	Yengo	COJO	Yes
rs1075901	17	15943910	T	C	0.436	-0.013	0.002	2.08713e-15	BMI	Yengo	COJO	Yes
rs4516268	17	1846831	A	C	0.192	-0.019	0.002	6.87764e-19	BMI	Yengo	COJO	No
rs4986044	17	21261560	T	C	0.469	-0.016	0.002	5.61224e-23	BMI	Yengo	COJO	No
rs7217226	17	2136065	T	G	0.640	-0.011	0.002	1.27487e-10	BMI	Yengo	COJO	Yes
rs1038088	17	28074563	T	G	0.492	-0.013	0.002	1.22424e-14	BMI	Yengo	COJO	Yes
rs8067737	17	29349688	T	C	0.110	0.017	0.003	6.79784e-09	BMI	Yengo	COJO	Yes
rs7211567	17	31460899	T	C	0.220	-0.015	0.002	3.72248e-13	BMI	Yengo	COJO	No
rs12453418	17	31747629	A	G	0.652	-0.011	0.002	1.85057e-09	BMI	Yengo	COJO	No
rs1106908	17	34942595	A	G	0.441	-0.016	0.002	8.61506e-22	BMI	Yengo	COJO	Yes
rs4796243	17	35057883	A	G	0.303	-0.013	0.002	4.45369e-11	BMI	Yengo	COJO	No
rs8070454	17	38160754	T	C	0.387	-0.010	0.002	9.87203e-09	BMI	Yengo	COJO	Yes

rs16966801	17	39573713	A	G	0.798	-0.014	0.002	1.64914e-10	BMI	Yengo	COJO	No
rs8069296	17	42935059	T	C	0.793	-0.013	0.002	7.7217e-10	BMI	Yengo	COJO	Yes
rs886444	17	46051911	A	G	0.396	-0.013	0.002	5.63497e-12	BMI	Yengo	COJO	No
rs208015	17	46252346	T	C	0.078	0.031	0.004	1.52001e-18	BMI	Yengo	COJO	Yes
rs9299	17	46669430	T	C	0.647	0.015	0.002	2.61814e-15	BMI	Yengo	COJO	Yes
rs11079849	17	47090785	T	C	0.320	-0.015	0.002	2.9655e-13	BMI	Yengo	COJO	Yes
rs10515050	17	51923847	T	C	0.415	-0.010	0.002	9.85212e-09	BMI	Yengo	COJO	No
rs1000940	17	5283252	A	G	0.701	-0.011	0.002	7.62249e-10	BMI	Yengo	COJO	Yes
rs8079034	17	5412361	T	C	0.188	0.014	0.002	4.91741e-09	BMI	Yengo	COJO	Yes
rs8071182	17	55336155	A	G	0.174	0.013	0.002	1.14052e-09	BMI	Yengo	COJO	Yes
rs757608	17	59497277	A	G	0.338	-0.010	0.002	6.77001e-09	BMI	Yengo	COJO	Yes
rs8075273	17	61728881	A	C	0.282	-0.011	0.002	1.15235e-09	BMI	Yengo	COJO	No
rs2537847	17	65694355	A	G	0.244	-0.012	0.002	3.39351e-09	BMI	Yengo	COJO	Yes
rs12602912	17	65870073	T	C	0.205	0.018	0.002	4.77727e-18	BMI	Yengo	COJO	Yes
rs2619976	17	71754545	T	C	0.413	0.011	0.002	4.27641e-09	BMI	Yengo	COJO	No
rs7209235	17	73759552	A	G	0.695	-0.012	0.002	5.34822e-10	BMI	Yengo	COJO	No
rs8081039	17	75995829	T	C	0.057	0.024	0.004	2.83219e-10	BMI	Yengo	COJO	No

rs1285245	17	77796889	C	G	0.367	-0.012	0.002	4.18868e-11	BMI	Yengo	COJO	Yes
rs12939549	17	78611724	A	G	0.566	0.016	0.002	9.86802e-24	BMI	Yengo	COJO	Yes
rs4889782	17	78640510	T	C	0.602	-0.012	0.002	2.39518e-11	BMI	Yengo	COJO	Yes
rs4969387	17	79081724	C	G	0.746	-0.017	0.002	1.80783e-15	BMI	Yengo	COJO	Yes
rs1048775	17	79202329	C	G	0.480	0.012	0.002	1.19174e-09	BMI	Yengo	COJO	Yes
rs9905991	17	80052073	A	G	0.448	0.011	0.002	6.25724e-10	BMI	Yengo	COJO	Yes
rs17681708	17	9792872	T	C	0.688	-0.010	0.002	8.65208e-09	BMI	Yengo	COJO	No
rs8097544	18	1839564	A	G	0.848	-0.021	0.003	3.34685e-17	BMI	Yengo	COJO	Yes
rs12964689	18	21116998	A	G	0.518	0.023	0.002	1.88346e-38	BMI	Yengo	COJO	No
rs273697	18	23178748	A	G	0.478	-0.011	0.002	4.0629e-10	BMI	Yengo	COJO	No
rs1941697	18	31251276	A	G	0.454	0.014	0.002	1.9903e-15	BMI	Yengo	COJO	No
rs16965062	18	31581247	T	C	0.430	0.010	0.002	8.19529e-09	BMI	Yengo	COJO	Yes
rs1365466	18	36182440	T	C	0.741	-0.015	0.002	2.9061e-14	BMI	Yengo	COJO	Yes
rs1791253	18	37103550	T	G	0.063	0.022	0.004	3.11085e-09	BMI	Yengo	COJO	Yes
rs555267	18	40992698	T	G	0.330	0.011	0.002	1.13381e-09	BMI	Yengo	COJO	Yes
rs954018	18	42598463	A	G	0.305	-0.014	0.002	9.64715e-15	BMI	Yengo	COJO	No
rs10438964	18	42950629	T	C	0.276	-0.014	0.002	5.78108e-13	BMI	Yengo	COJO	Yes

rs7239114	18	45921214	A	G	0.540	0.012	0.002	1.10487e-12	BMI	Yengo	COJO	Yes
rs1498139	18	51478026	A	C	0.727	0.013	0.002	3.6834e-10	BMI	Yengo	COJO	Yes
rs8092503	18	52479487	A	G	0.768	-0.014	0.002	4.53466e-12	BMI	Yengo	COJO	Yes
rs11659764	18	53335512	A	T	0.053	-0.030	0.004	2.0299e-13	BMI	Yengo	COJO	No
rs7243357	18	56883319	T	G	0.827	0.021	0.002	2.24659e-23	BMI	Yengo	COJO	No
rs2000746	18	57677294	A	G	0.734	0.015	0.002	3.54772e-13	BMI	Yengo	COJO	Yes
rs12327272	18	57726627	A	G	0.114	0.028	0.003	1.81277e-16	BMI	Yengo	COJO	No
rs1942866	18	57741783	C	G	0.624	0.019	0.003	1.33953e-09	BMI	Yengo	COJO	Yes
rs8095404	18	57804346	A	T	0.544	-0.040	0.003	1.17398e-31	BMI	Yengo	COJO	Yes
rs663129	18	57838401	A	G	0.230	0.033	0.003	1.92151e-32	BMI	Yengo	COJO	Yes
rs9961813	18	57853056	A	C	0.913	0.045	0.004	5.29267e-25	BMI	Yengo	COJO	Yes
rs8094523	18	57878155	A	G	0.080	-0.044	0.004	5.72846e-30	BMI	Yengo	COJO	Yes
rs9675376	18	57969244	A	G	0.288	0.022	0.002	1.29341e-22	BMI	Yengo	COJO	Yes
rs2229616	18	58039276	T	C	0.020	-0.125	0.006	4.05929e-83	BMI	Yengo	COJO	Yes
rs8087550	18	58371566	A	C	0.492	0.013	0.002	1.35203e-09	BMI	Yengo	COJO	Yes
rs9951893	18	60739250	T	C	0.525	-0.011	0.002	3.09961e-10	BMI	Yengo	COJO	Yes

rs2012927	18	63297672	A	G	0.335	0.011	0.002	2.37185e-09	BMI	Yengo	COJO	No
rs1241986	18	6873954	A	G	0.848	-0.015	0.002	6.14239e-10	BMI	Yengo	COJO	Yes
rs8089514	18	69224478	A	T	0.359	0.014	0.002	2.95531e-12	BMI	Yengo	COJO	Yes
rs11150911	18	73498528	A	C	0.281	0.014	0.002	2.06926e-14	BMI	Yengo	COJO	No
rs1787267	18	76742544	C	G	0.063	-0.024	0.004	2.75616e-11	BMI	Yengo	COJO	Yes
rs1608445	18	947954	A	G	0.435	-0.010	0.002	7.89179e-09	BMI	Yengo	COJO	No
rs12609744	19	12994140	T	C	0.693	-0.013	0.002	1.99225e-11	BMI	Yengo	COJO	Yes
rs273504	19	18215247	A	G	0.573	-0.013	0.002	3.61053e-13	BMI	Yengo	COJO	No
rs17724992	19	18454825	A	G	0.740	0.018	0.002	1.92439e-20	BMI	Yengo	COJO	No
rs757318	19	18820308	A	C	0.480	-0.015	0.002	2.64389e-17	BMI	Yengo	COJO	Yes
rs998732	19	19378671	A	G	0.842	0.016	0.002	4.33124e-13	BMI	Yengo	COJO	No
rs2304130	19	19789528	A	G	0.915	0.021	0.004	1.71319e-09	BMI	Yengo	COJO	Yes
rs8102137	19	30296853	T	C	0.676	-0.019	0.002	4.00942e-25	BMI	Yengo	COJO	No
rs2866816	19	30683879	T	C	0.739	0.012	0.002	4.08049e-09	BMI	Yengo	COJO	Yes
rs11668301	19	31016196	A	G	0.848	0.017	0.002	6.81275e-13	BMI	Yengo	COJO	No
rs10408013	19	33963766	T	C	0.291	0.013	0.002	1.3764e-12	BMI	Yengo	COJO	Yes
rs29938	19	34311481	T	C	0.328	-0.013	0.002	7.03995e-14	BMI	Yengo	COJO	Yes

rs895330	19	4060707	C	G	0.808	0.020	0.002	7.79218e-18	BMI	Yengo	COJO	No
rs3826705	19	42637232	T	C	0.879	-0.016	0.003	6.07529e-09	BMI	Yengo	COJO	No
rs2075650	19	45395619	A	G	0.861	0.022	0.002	3.73557e-22	BMI	Yengo	COJO	No
rs11672660	19	46180184	T	C	0.205	-0.035	0.002	1.97888e-56	BMI	Yengo	COJO	Yes
rs3810291	19	47569003	A	G	0.670	0.029	0.002	1.13367e-45	BMI	Yengo	COJO	Yes
rs1884389	20	1410582	T	C	0.429	-0.011	0.002	1.78437e-10	BMI	Yengo	COJO	No
rs1040881	20	15099816	T	C	0.674	0.011	0.002	1.48839e-09	BMI	Yengo	COJO	Yes
rs12480713	20	15801600	T	C	0.564	0.013	0.002	8.6833e-11	BMI	Yengo	COJO	Yes
rs8123881	20	15819495	A	G	0.870	-0.022	0.002	2.14973e-19	BMI	Yengo	COJO	No
rs4814512	20	16564210	A	C	0.782	0.016	0.002	2.44374e-13	BMI	Yengo	COJO	Yes
rs6138482	20	25059442	T	C	0.197	0.020	0.002	8.76824e-19	BMI	Yengo	COJO	No
rs6076348	20	25401827	A	G	0.692	-0.023	0.003	2.09774e-14	BMI	Yengo	COJO	Yes
rs2386802	20	25971327	A	C	0.668	-0.025	0.003	5.84991e-18	BMI	Yengo	COJO	Yes
rs6132918	20	26073030	T	C	0.823	-0.023	0.003	2.80217e-15	BMI	Yengo	COJO	Yes
rs816533	20	26256565	A	G	0.962	-0.031	0.005	6.14267e-10	BMI	Yengo	COJO	Yes
rs753010	20	29857455	C	G	0.949	-0.044	0.006	1.69264e-13	BMI	Yengo	COJO	No
rs6061162	20	29893501	T	C	0.913	0.050	0.005	7.69803e-21	BMI	Yengo	COJO	Yes

rs676749	20	3026069	A	T	0.502	-0.013	0.002	2.78533e-12	BMI	Yengo	COJO	No
rs8121840	20	30504530	A	G	0.493	0.010	0.002	4.18059e-09	BMI	Yengo	COJO	Yes
rs6121381	20	30785593	A	T	0.847	-0.026	0.003	1.75709e-19	BMI	Yengo	COJO	Yes
rs6058635	20	30891925	C	G	0.434	0.027	0.003	3.09405e-18	BMI	Yengo	COJO	Yes
rs293566	20	31097877	T	C	0.653	-0.016	0.002	2.11507e-11	BMI	Yengo	COJO	Yes
rs13041173	20	32542814	A	G	0.659	-0.056	0.004	8.50076e-36	BMI	Yengo	COJO	Yes
rs17091470	20	32606299	T	G	0.925	-0.051	0.005	1.14212e-24	BMI	Yengo	COJO	Yes
rs6142096	20	32686658	A	G	0.528	0.020	0.003	1.33266e-11	BMI	Yengo	COJO	Yes
rs1015363	20	32738335	A	G	0.556	0.034	0.004	1.76219e-20	BMI	Yengo	COJO	Yes
rs1015362	20	32738612	T	C	0.287	0.020	0.003	5.38243e-09	BMI	Yengo	COJO	No
rs6088529	20	33170752	A	C	0.342	0.049	0.004	4.00906e-41	BMI	Yengo	COJO	Yes
rs6060151	20	33594226	T	G	0.632	-0.062	0.004	4.31417e-47	BMI	Yengo	COJO	Yes
rs13045538	20	33595525	T	C	0.960	-0.066	0.007	5.71864e-24	BMI	Yengo	COJO	Yes
rs3746429	20	33703607	T	C	0.173	0.067	0.005	6.23545e-47	BMI	Yengo	COJO	Yes
rs143384	20	34025756	A	G	0.589	0.015	0.002	9.65034e-14	BMI	Yengo	COJO	Yes
rs6088943	20	34420023	A	T	0.939	0.025	0.004	4.41703e-11	BMI	Yengo	COJO	No

rs2425241	20	35018412	T	C	0.067	-0.024	0.004	5.59489e-12	BMI	Yengo	COJO	Yes
rs2143253	20	41987392	A	G	0.119	-0.019	0.003	3.95779e-13	BMI	Yengo	COJO	Yes
rs2425857	20	44914134	A	G	0.441	0.014	0.002	1.14442e-15	BMI	Yengo	COJO	No
rs6019482	20	47495560	T	C	0.165	-0.018	0.002	3.05175e-15	BMI	Yengo	COJO	Yes
rs17806379	20	51107290	T	C	0.179	-0.025	0.002	2.1529e-27	BMI	Yengo	COJO	No
rs1512065	20	53453326	A	G	0.237	0.014	0.002	6.67444e-12	BMI	Yengo	COJO	Yes
rs559267	20	54157497	A	G	0.664	-0.013	0.002	2.33674e-13	BMI	Yengo	COJO	No
rs6011457	20	61530915	A	T	0.498	-0.012	0.002	6.47994e-12	BMI	Yengo	COJO	Yes
rs310618	20	62127121	T	C	0.671	-0.012	0.002	4.84413e-11	BMI	Yengo	COJO	No
rs12625413	20	62380542	T	C	0.655	-0.011	0.002	1.86282e-09	BMI	Yengo	COJO	Yes
rs8567	20	62522315	A	G	0.523	-0.010	0.002	1.7702e-09	BMI	Yengo	COJO	Yes
rs1884897	20	6612832	A	G	0.369	-0.019	0.002	3.07094e-29	BMI	Yengo	COJO	No
rs9979651	21	34153330	C	G	0.929	-0.021	0.004	2.57236e-09	BMI	Yengo	COJO	No
rs762147	21	39238610	A	G	0.271	-0.012	0.002	1.29944e-10	BMI	Yengo	COJO	Yes
rs13047416	21	40309436	C	G	0.623	0.012	0.002	5.75696e-10	BMI	Yengo	COJO	No
rs2836961	21	40627020	A	C	0.616	-0.012	0.002	1.02551e-11	BMI	Yengo	COJO	Yes
rs2838006	21	42653567	T	C	0.362	-0.013	0.002	2.39134e-12	BMI	Yengo	COJO	Yes

rs427943	21	46570896	A	C	0.433	-0.017	0.002	1.1523e-20	BMI	Yengo	COJO	No
rs4820408	22	40604945	T	G	0.408	0.020	0.002	9.86739e-25	BMI	Yengo	COJO	No
rs5750913	22	40640285	A	G	0.754	-0.013	0.002	7.05749e-09	BMI	Yengo	COJO	Yes
rs9615905	22	48875699	T	C	0.450	0.010	0.002	2.57041e-09	BMI	Yengo	COJO	No
rs1730859	1	107617707	A	G	0.658	-0.012	0.002	1.1e-11	BMI	Yengo	non-COJO	No
rs12035149	1	107885018	C	G	0.777	-0.015	0.002	3.9e-12	BMI	Yengo	non-COJO	Yes
rs17531363	1	107977075	A	C	0.697	0.013	0.002	2e-12	BMI	Yengo	non-COJO	Yes
rs7550711	1	110082886	T	C	0.031	0.065	0.005	3.2e-38	BMI	Yengo	non-COJO	No
rs12033257	1	112318484	A	G	0.616	0.015	0.002	2.4e-15	BMI	Yengo	non-COJO	Yes
rs10779751	1	11284336	A	G	0.274	0.014	0.002	2.5e-14	BMI	Yengo	non-COJO	Yes
rs12731372	1	118852975	T	C	0.232	0.012	0.002	1.2e-09	BMI	Yengo	non-COJO	Yes
rs10923724	1	119546842	T	C	0.572	-0.012	0.002	6.4e-13	BMI	Yengo	non-COJO	Yes
rs6587552	1	151018861	A	G	0.241	0.017	0.002	1.6e-17	BMI	Yengo	non-COJO	No
rs905938	1	154991389	T	C	0.732	-0.015	0.002	1.2e-15	BMI	Yengo	non-COJO	Yes
rs11577179	1	155983710	A	G	0.372	-0.011	0.002	1.5e-10	BMI	Yengo	non-COJO	Yes
rs10733051	1	167280354	A	G	0.520	0.010	0.002	2.9e-09	BMI	Yengo	non-COJO	No
rs12044597	1	1708801	A	G	0.497	-0.014	0.002	1.7e-18	BMI	Yengo	non-COJO	No

rs761423	1	17301672	T	C	0.550	0.011	0.002	5.5e-11	BMI	Yengo	non-COJO	No
rs12564992	1	174478100	A	G	0.886	-0.020	0.003	5.3e-14	BMI	Yengo	non-COJO	No
rs6700816	1	174883994	A	T	0.968	0.034	0.005	8.9e-12	BMI	Yengo	non-COJO	Yes
rs543874	1	177889480	A	G	0.805	-0.048	0.002	1.2e-122	BMI	Yengo	non-COJO	No
rs10920678	1	190239907	A	G	0.429	0.016	0.002	1.5e-21	BMI	Yengo	non-COJO	No
rs12041258	1	195047936	T	C	0.771	0.015	0.002	9.5e-13	BMI	Yengo	non-COJO	No
rs10754210	1	197012111	A	G	0.311	-0.012	0.002	3.2e-11	BMI	Yengo	non-COJO	Yes
rs2820311	1	201841476	A	G	0.663	-0.024	0.002	4.1e-38	BMI	Yengo	non-COJO	No
rs9077	1	202116238	A	G	0.330	-0.014	0.002	3.5e-13	BMI	Yengo	non-COJO	Yes
rs823074	1	205774839	T	C	0.588	0.011	0.002	1.6e-10	BMI	Yengo	non-COJO	No
rs17014375	1	209543560	T	G	0.865	-0.017	0.002	1.1e-11	BMI	Yengo	non-COJO	Yes
rs11118308	1	219633869	A	G	0.530	0.010	0.002	4.8e-10	BMI	Yengo	non-COJO	No
rs10915840	1	225668524	A	G	0.283	-0.012	0.002	1.3e-09	BMI	Yengo	non-COJO	No
rs967605	1	23399932	T	C	0.833	-0.019	0.002	1.7e-16	BMI	Yengo	non-COJO	No
rs2491864	1	242986063	A	G	0.215	0.014	0.002	7.3e-11	BMI	Yengo	non-COJO	No
rs12042959	1	243533273	A	G	0.850	0.014	0.002	3.4e-09	BMI	Yengo	non-COJO	No

rs3753549	1	243722892	T	C	0.856	-0.020	0.002	1.7e-15	BMI	Yengo	non-COJO	Yes
rs7535528	1	2444414	A	G	0.374	-0.015	0.002	1.4e-16	BMI	Yengo	non-COJO	No
rs785278	1	33307987	A	T	0.177	-0.016	0.002	2.8e-12	BMI	Yengo	non-COJO	No
rs4653017	1	33776728	T	C	0.682	0.012	0.002	4.5e-11	BMI	Yengo	non-COJO	Yes
rs9426003	1	34602870	A	G	0.295	-0.012	0.002	1.4e-09	BMI	Yengo	non-COJO	No
rs11583122	1	38053458	T	C	0.079	0.018	0.003	7.4e-10	BMI	Yengo	non-COJO	Yes
rs2282231	1	39569571	T	C	0.225	0.016	0.002	4.8e-15	BMI	Yengo	non-COJO	Yes
rs946526	1	46487168	T	C	0.043	-0.031	0.004	1.7e-13	BMI	Yengo	non-COJO	No
rs2275426	1	46487552	A	G	0.434	0.010	0.002	2e-10	BMI	Yengo	non-COJO	Yes
rs6700838	1	47700027	T	C	0.596	-0.017	0.002	2.5e-22	BMI	Yengo	non-COJO	Yes
rs7531656	1	49828663	A	G	0.325	0.020	0.002	7.4e-29	BMI	Yengo	non-COJO	Yes
rs2356865	1	50836334	T	C	0.295	-0.011	0.002	1.6e-09	BMI	Yengo	non-COJO	No
rs2481665	1	62594677	T	C	0.559	0.016	0.002	7.2e-23	BMI	Yengo	non-COJO	No
rs11208662	1	65987164	C	G	0.088	0.021	0.003	2e-11	BMI	Yengo	non-COJO	Yes
rs6577584	1	6715390	T	G	0.654	-0.013	0.002	3.7e-13	BMI	Yengo	non-COJO	No
rs7531118	1	72837239	T	C	0.460	-0.026	0.002	3.6e-54	BMI	Yengo	non-COJO	No
rs2590942	1	72885281	T	G	0.816	0.029	0.002	1.2e-46	BMI	Yengo	non-COJO	Yes

rs12042908	1	74997762	A	G	0.436	0.018	0.002	1.4e-29	BMI	Yengo	non-COJO	Yes
rs12035349	1	77557339	A	G	0.870	-0.019	0.003	1.1e-12	BMI	Yengo	non-COJO	Yes
rs17391694	1	78623626	T	C	0.119	0.032	0.002	7.5e-38	BMI	Yengo	non-COJO	Yes
rs2154297	1	80791708	T	C	0.712	-0.012	0.002	1.2e-09	BMI	Yengo	non-COJO	Yes
rs284227	1	82379446	T	C	0.745	-0.015	0.002	3.5e-15	BMI	Yengo	non-COJO	No
rs7556169	1	8741401	A	G	0.386	-0.010	0.002	5.4e-09	BMI	Yengo	non-COJO	Yes
rs6690764	1	92976590	A	G	0.792	-0.015	0.002	6.3e-12	BMI	Yengo	non-COJO	No
rs1973993	1	96943994	T	C	0.410	-0.021	0.002	4.7e-33	BMI	Yengo	non-COJO	Yes
rs2030342	1	97388226	T	C	0.575	0.014	0.002	1.9e-16	BMI	Yengo	non-COJO	No
rs4372296	1	98320492	A	C	0.771	-0.013	0.002	7.6e-11	BMI	Yengo	non-COJO	Yes
rs4303732	2	100830040	T	C	0.603	0.014	0.002	2.2e-16	BMI	Yengo	non-COJO	No
rs6711584	2	104421692	A	G	0.454	0.013	0.002	2.2e-13	BMI	Yengo	non-COJO	No
rs1451533	2	105466005	A	G	0.273	0.017	0.002	1e-17	BMI	Yengo	non-COJO	Yes
rs902695	2	113955074	A	G	0.480	-0.010	0.002	2.2e-09	BMI	Yengo	non-COJO	No
rs17551974	2	142293146	A	C	0.178	-0.014	0.002	1.9e-10	BMI	Yengo	non-COJO	No
rs2890652	2	142959931	T	C	0.824	-0.017	0.002	2.5e-13	BMI	Yengo	non-COJO	Yes
rs6710871	2	143960593	A	G	0.142	0.018	0.002	1e-13	BMI	Yengo	non-COJO	No

rs7560871	2	145616899	A	G	0.073	0.022	0.003	9.6e-11	BMI	Yengo	non-COJO	Yes
rs453520	2	147907202	T	C	0.583	-0.015	0.002	7e-18	BMI	Yengo	non-COJO	Yes
rs16828086	2	151198990	C	G	0.617	0.010	0.002	1e-08	BMI	Yengo	non-COJO	Yes
rs7600699	2	156018263	C	G	0.842	-0.015	0.002	6.4e-10	BMI	Yengo	non-COJO	No
rs6738445	2	172599615	T	C	0.284	-0.013	0.002	1.9e-13	BMI	Yengo	non-COJO	No
rs10930641	2	175000711	A	G	0.591	-0.014	0.002	3.6e-15	BMI	Yengo	non-COJO	No
rs9630985	2	181607676	A	C	0.324	-0.018	0.002	4.4e-22	BMI	Yengo	non-COJO	Yes
rs10497807	2	198585087	C	G	0.520	-0.011	0.002	1.5e-11	BMI	Yengo	non-COJO	No
rs7564679	2	204012790	A	G	0.428	-0.012	0.002	1.3e-12	BMI	Yengo	non-COJO	No
rs12694021	2	206084372	A	C	0.448	0.011	0.002	1e-09	BMI	Yengo	non-COJO	No
rs972540	2	207244783	A	G	0.727	-0.013	0.002	8e-13	BMI	Yengo	non-COJO	Yes
rs17203016	2	208255518	A	G	0.804	-0.015	0.002	2.1e-13	BMI	Yengo	non-COJO	Yes
rs4673553	2	211608379	T	G	0.544	-0.014	0.002	2.1e-16	BMI	Yengo	non-COJO	No
rs1437929	2	211983316	A	G	0.288	0.014	0.002	9.9e-13	BMI	Yengo	non-COJO	Yes
rs7599312	2	213413231	A	G	0.265	-0.019	0.002	6.9e-24	BMI	Yengo	non-COJO	Yes
rs7607369	2	219279097	A	G	0.439	0.012	0.002	9.3e-13	BMI	Yengo	non-COJO	Yes

rs11889536	2	220163543	A	G	0.851	0.019	0.002	6.4e-15	BMI	Yengo	non-COJO	Yes
rs12479233	2	228891702	A	T	0.487	-0.012	0.002	1.6e-12	BMI	Yengo	non-COJO	No
rs10211055	2	229016917	T	C	0.654	-0.016	0.002	7.2e-18	BMI	Yengo	non-COJO	Yes
rs6720868	2	230663576	T	C	0.329	0.016	0.002	5.1e-17	BMI	Yengo	non-COJO	Yes
rs10182181	2	25150296	A	G	0.525	-0.032	0.002	6.7e-90	BMI	Yengo	non-COJO	No
rs4372836	2	28973883	T	C	0.303	0.014	0.002	7.3e-16	BMI	Yengo	non-COJO	Yes
rs6548221	2	295255	A	G	0.225	0.015	0.002	1.7e-14	BMI	Yengo	non-COJO	No
rs17327461	2	35512183	T	C	0.450	0.012	0.002	1.5e-14	BMI	Yengo	non-COJO	No
rs4670626	2	37046657	T	C	0.357	-0.011	0.002	4.9e-10	BMI	Yengo	non-COJO	No
rs6713781	2	40291940	C	G	0.414	-0.012	0.002	3.8e-12	BMI	Yengo	non-COJO	Yes
rs4639527	2	416815	A	G	0.699	-0.017	0.002	3.3e-20	BMI	Yengo	non-COJO	Yes
rs17035438	2	46878616	A	G	0.094	0.020	0.003	3.3e-11	BMI	Yengo	non-COJO	No
rs7561278	2	48954905	T	C	0.786	0.016	0.002	5.7e-14	BMI	Yengo	non-COJO	No
rs930295	2	50233352	A	C	0.158	0.021	0.002	1e-19	BMI	Yengo	non-COJO	Yes
rs7598402	2	50735943	C	G	0.510	0.012	0.002	2.1e-12	BMI	Yengo	non-COJO	No
rs7601895	2	55281901	C	G	0.704	0.015	0.002	1.7e-15	BMI	Yengo	non-COJO	Yes
rs13432055	2	56603985	T	C	0.714	-0.012	0.002	8.9e-11	BMI	Yengo	non-COJO	Yes

rs929641	2	58792377	A	G	0.584	0.015	0.002	4.8e-20	BMI	Yengo	non-COJO	Yes
rs4671328	2	58935282	T	G	0.447	0.022	0.002	2.2e-36	BMI	Yengo	non-COJO	No
rs6545714	2	59307725	A	G	0.614	-0.019	0.002	9.1e-31	BMI	Yengo	non-COJO	No
rs4671358	2	60164634	A	T	0.596	0.010	0.002	6.7e-09	BMI	Yengo	non-COJO	No
rs980329	2	60285100	T	C	0.752	-0.013	0.002	2.5e-11	BMI	Yengo	non-COJO	Yes
rs10929925	2	6155557	A	C	0.430	-0.014	0.002	1.8e-18	BMI	Yengo	non-COJO	Yes
rs13417156	2	62848319	T	C	0.564	-0.014	0.002	2.6e-17	BMI	Yengo	non-COJO	Yes
rs13021737	2	632348	A	G	0.168	-0.057	0.002	7.5e-157	BMI	Yengo	non-COJO	Yes
rs7607351	2	69562127	T	C	0.581	0.012	0.002	8.4e-12	BMI	Yengo	non-COJO	No
rs934515	2	79482643	A	G	0.118	0.018	0.003	7.6e-12	BMI	Yengo	non-COJO	Yes
rs1371108	2	81816251	A	C	0.325	0.012	0.002	9e-11	BMI	Yengo	non-COJO	No
rs7557796	2	86766153	T	C	0.348	0.016	0.002	2.3e-19	BMI	Yengo	non-COJO	No
rs1436343	3	104606130	A	G	0.408	-0.014	0.002	7.3e-16	BMI	Yengo	non-COJO	No
rs13321566	3	107342662	A	G	0.816	-0.014	0.002	4.7e-09	BMI	Yengo	non-COJO	Yes
rs7640424	3	107820063	T	C	0.297	-0.014	0.002	2.3e-14	BMI	Yengo	non-COJO	No
rs4273371	3	108119071	T	C	0.502	-0.012	0.002	1.2e-12	BMI	Yengo	non-COJO	Yes
rs17681451	3	114399296	A	G	0.084	-0.020	0.003	3.5e-10	BMI	Yengo	non-COJO	No

rs6804181	3	116937546	A	T	0.821	0.015	0.002	5.5e-11	BMI	Yengo	non-COJO	Yes
rs4624596	3	119571541	T	C	0.815	0.014	0.002	2.2e-09	BMI	Yengo	non-COJO	No
rs2124499	3	123093541	C	G	0.372	-0.012	0.002	3.4e-13	BMI	Yengo	non-COJO	Yes
rs1899951	3	12394840	T	C	0.131	0.017	0.002	3.1e-12	BMI	Yengo	non-COJO	No
rs1909586	3	124687767	T	G	0.598	-0.011	0.002	4.8e-09	BMI	Yengo	non-COJO	Yes
rs9809534	3	125189782	C	G	0.877	0.016	0.003	2.3e-10	BMI	Yengo	non-COJO	Yes
rs1320903	3	131758077	A	G	0.317	0.022	0.002	9.2e-32	BMI	Yengo	non-COJO	No
rs580438	3	13345450	T	C	0.332	0.011	0.002	6.5e-10	BMI	Yengo	non-COJO	Yes
rs10935143	3	134665159	A	G	0.454	-0.011	0.002	2.8e-10	BMI	Yengo	non-COJO	No
rs6786582	3	135898984	T	C	0.726	-0.016	0.002	7.5e-18	BMI	Yengo	non-COJO	No
rs16851483	3	141275436	T	G	0.069	0.037	0.004	3.2e-26	BMI	Yengo	non-COJO	Yes
rs355777	3	154034950	C	G	0.411	0.015	0.002	1.4e-18	BMI	Yengo	non-COJO	No
rs7615297	3	156299313	C	G	0.854	0.015	0.002	5.7e-10	BMI	Yengo	non-COJO	No
rs6767619	3	156893782	C	G	0.345	0.012	0.002	8.1e-11	BMI	Yengo	non-COJO	Yes
rs827092	3	157985182	T	C	0.583	0.013	0.002	1.1e-13	BMI	Yengo	non-COJO	Yes
rs11128760	3	15873407	A	G	0.403	0.011	0.002	3.1e-10	BMI	Yengo	non-COJO	No

rs5396	3	170744815	T	C	0.724	-0.015	0.002	3e-17	BMI	Yengo	non-COJO	No
rs39654	3	173095123	A	G	0.445	-0.014	0.002	6.5e-17	BMI	Yengo	non-COJO	Yes
rs6443750	3	181329682	T	C	0.193	-0.015	0.002	3.2e-12	BMI	Yengo	non-COJO	No
rs262956	3	183486117	T	G	0.347	0.012	0.002	6.1e-12	BMI	Yengo	non-COJO	Yes
rs2293605	3	184044433	T	C	0.131	-0.017	0.003	3.6e-10	BMI	Yengo	non-COJO	No
rs9816226	3	185834499	A	T	0.180	-0.032	0.002	1.6e-52	BMI	Yengo	non-COJO	Yes
rs6764533	3	196088464	A	G	0.359	0.012	0.002	1.4e-10	BMI	Yengo	non-COJO	No
rs4858193	3	20441050	T	C	0.722	0.013	0.002	1.6e-11	BMI	Yengo	non-COJO	Yes
rs6804842	3	25106437	A	G	0.428	-0.016	0.002	3.6e-21	BMI	Yengo	non-COJO	Yes
rs9814633	3	41310470	A	G	0.343	0.012	0.002	2.1e-11	BMI	Yengo	non-COJO	No
rs10460960	3	42308735	A	G	0.888	0.020	0.002	8.1e-15	BMI	Yengo	non-COJO	Yes
rs28350	3	42418446	A	G	0.193	0.018	0.002	3.5e-15	BMI	Yengo	non-COJO	Yes
rs6442101	3	48130893	T	C	0.682	-0.012	0.002	2.5e-11	BMI	Yengo	non-COJO	No
rs3731544	3	48207997	A	C	0.071	0.021	0.003	7.5e-12	BMI	Yengo	non-COJO	Yes
rs2230590	3	49936102	T	C	0.492	-0.024	0.002	4.1e-44	BMI	Yengo	non-COJO	No
rs12631248	3	50080174	C	G	0.922	-0.025	0.003	3e-17	BMI	Yengo	non-COJO	Yes
rs9838283	3	50820486	A	G	0.798	0.016	0.003	1e-09	BMI	Yengo	non-COJO	Yes

rs2710323	3	52815905	T	C	0.520	-0.014	0.002	4.8e-18	BMI	Yengo	non-COJO	Yes
rs2680648	3	53777176	T	C	0.765	0.016	0.002	3.8e-15	BMI	Yengo	non-COJO	Yes
rs12488237	3	56114861	T	C	0.948	-0.024	0.004	4.5e-11	BMI	Yengo	non-COJO	Yes
rs2365389	3	61236462	T	C	0.414	-0.017	0.002	1.3e-25	BMI	Yengo	non-COJO	No
rs1452075	3	62481063	T	C	0.728	0.014	0.002	1.3e-14	BMI	Yengo	non-COJO	No
rs925018	3	62713143	C	G	0.676	-0.013	0.002	1.4e-13	BMI	Yengo	non-COJO	No
rs11915371	3	70539559	A	C	0.796	-0.015	0.002	2.6e-12	BMI	Yengo	non-COJO	Yes
rs775731	3	77624784	T	C	0.588	-0.011	0.002	6.6e-10	BMI	Yengo	non-COJO	No
rs1554193	3	8138801	A	T	0.471	-0.010	0.002	4.4e-09	BMI	Yengo	non-COJO	No
rs3849570	3	81792112	A	C	0.341	0.013	0.002	3.3e-14	BMI	Yengo	non-COJO	Yes
rs10511093	3	83763541	T	C	0.074	-0.023	0.003	1.1e-11	BMI	Yengo	non-COJO	No
rs1375561	3	85658230	T	C	0.654	0.017	0.002	3.1e-24	BMI	Yengo	non-COJO	No
rs2122042	3	85866335	T	G	0.206	0.024	0.002	2.3e-31	BMI	Yengo	non-COJO	Yes
rs9714342	3	90428286	T	C	0.423	-0.015	0.002	6.1e-15	BMI	Yengo	non-COJO	Yes
rs1454687	3	94038085	C	G	0.477	0.020	0.002	5.2e-32	BMI	Yengo	non-COJO	No
rs3915844	3	9514856	A	G	0.143	0.015	0.002	2.2e-09	BMI	Yengo	non-COJO	Yes
rs2850969	4	102183594	T	C	0.857	-0.016	0.002	1.3e-11	BMI	Yengo	non-COJO	No

rs7377083	4	102708997	A	C	0.436	0.020	0.002	1.4e-27	BMI	Yengo	non-COJO	Yes
rs13107325	4	103188709	T	C	0.074	0.047	0.003	1.1e-47	BMI	Yengo	non-COJO	Yes
rs6843738	4	103936001	A	G	0.329	-0.011	0.002	7.2e-10	BMI	Yengo	non-COJO	Yes
rs326889	4	112713436	T	C	0.393	-0.013	0.002	2.4e-13	BMI	Yengo	non-COJO	No
rs7694732	4	115124089	A	G	0.562	0.010	0.002	8.7e-09	BMI	Yengo	non-COJO	No
rs4864201	4	130731284	T	C	0.353	0.014	0.002	1.5e-16	BMI	Yengo	non-COJO	No
rs1296328	4	137083193	A	C	0.434	0.018	0.002	4.9e-24	BMI	Yengo	non-COJO	No
rs769674	4	140881964	A	T	0.678	0.014	0.002	2.2e-13	BMI	Yengo	non-COJO	Yes
rs331949	4	143663206	T	C	0.627	-0.011	0.002	1e-10	BMI	Yengo	non-COJO	Yes
rs1455137	4	145986668	A	C	0.620	-0.011	0.002	4.4e-10	BMI	Yengo	non-COJO	Yes
rs11736228	4	147376805	A	T	0.741	0.014	0.002	4.1e-12	BMI	Yengo	non-COJO	No
rs6827083	4	153075491	A	G	0.569	-0.010	0.002	4.8e-09	BMI	Yengo	non-COJO	No
rs13110266	4	162129844	A	G	0.406	-0.012	0.002	1.9e-12	BMI	Yengo	non-COJO	No
rs17538472	4	163038241	T	C	0.191	0.013	0.002	4.2e-09	BMI	Yengo	non-COJO	Yes
rs1522569	4	171632637	T	G	0.818	0.016	0.002	2.9e-13	BMI	Yengo	non-COJO	No
rs7683836	4	180167906	A	G	0.540	-0.011	0.002	6.3e-11	BMI	Yengo	non-COJO	No

rs1477887	4	18514827	A	G	0.457	-0.014	0.002	2e-15	BMI	Yengo	non-COJO	No
rs1323068	4	20263058	A	G	0.321	-0.011	0.002	6.9e-10	BMI	Yengo	non-COJO	Yes
rs9291467	4	25428296	T	C	0.462	0.014	0.002	6.7e-16	BMI	Yengo	non-COJO	No
rs6448587	4	28561990	A	C	0.811	0.017	0.002	2.3e-13	BMI	Yengo	non-COJO	No
rs1345148	4	30843533	T	C	0.603	-0.011	0.002	2.5e-10	BMI	Yengo	non-COJO	Yes
rs1000096	4	38692835	T	C	0.380	-0.014	0.002	1.8e-15	BMI	Yengo	non-COJO	No
rs1866510	4	44514468	T	C	0.350	-0.010	0.002	8.1e-09	BMI	Yengo	non-COJO	Yes
rs10938397	4	45182527	A	G	0.568	-0.032	0.002	3.4e-86	BMI	Yengo	non-COJO	Yes
rs2768950	4	49064487	A	G	0.251	0.012	0.002	7.5e-10	BMI	Yengo	non-COJO	No
rs711347	4	52926216	A	T	0.749	-0.012	0.002	4.5e-10	BMI	Yengo	non-COJO	Yes
rs2192158	4	55505360	A	G	0.460	0.013	0.002	8.3e-14	BMI	Yengo	non-COJO	Yes
rs925421	4	60253877	A	G	0.266	0.012	0.002	5.8e-09	BMI	Yengo	non-COJO	No
rs11945861	4	65700865	A	G	0.237	-0.015	0.002	5e-13	BMI	Yengo	non-COJO	Yes
rs7674623	4	80794681	T	C	0.198	0.014	0.002	5.7e-10	BMI	Yengo	non-COJO	No
rs4148155	4	89054667	A	G	0.887	0.019	0.003	5e-13	BMI	Yengo	non-COJO	Yes
rs1903579	4	91253956	C	G	0.550	0.011	0.002	1.1e-10	BMI	Yengo	non-COJO	No
rs7710595	5	106506697	A	C	0.534	0.010	0.002	5e-09	BMI	Yengo	non-COJO	No

rs40067	5	107439012	A	G	0.171	-0.027	0.002	7.1e-30	BMI	Yengo	non-COJO	Yes
rs6595205	5	119372533	C	G	0.470	0.011	0.002	2e-12	BMI	Yengo	non-COJO	No
rs7711753	5	122733317	A	G	0.436	-0.013	0.002	3.4e-16	BMI	Yengo	non-COJO	No
rs6877851	5	130356413	C	G	0.234	-0.012	0.002	8.8e-10	BMI	Yengo	non-COJO	Yes
rs329124	5	133865452	A	G	0.577	0.013	0.002	5.3e-14	BMI	Yengo	non-COJO	No
rs7716275	5	137631073	T	G	0.193	-0.013	0.002	2.2e-10	BMI	Yengo	non-COJO	No
rs13174863	5	139080745	A	G	0.845	-0.019	0.002	2.9e-16	BMI	Yengo	non-COJO	Yes
rs2190788	5	144484261	T	G	0.311	0.014	0.002	2.9e-14	BMI	Yengo	non-COJO	No
rs10066835	5	151254297	T	C	0.016	0.043	0.007	6.5e-09	BMI	Yengo	non-COJO	Yes
rs7715256	5	153537893	T	G	0.578	-0.017	0.002	2.2e-24	BMI	Yengo	non-COJO	Yes
rs17056301	5	158271680	T	C	0.736	-0.012	0.002	2.4e-09	BMI	Yengo	non-COJO	No
rs248139	5	167352783	A	G	0.193	0.013	0.002	1.2e-09	BMI	Yengo	non-COJO	No
rs7730898	5	170459675	A	G	0.729	0.017	0.002	4.5e-20	BMI	Yengo	non-COJO	Yes
rs4518345	5	27185904	A	G	0.284	-0.012	0.002	1e-09	BMI	Yengo	non-COJO	No
rs7730004	5	43191033	T	C	0.669	0.015	0.002	9.1e-16	BMI	Yengo	non-COJO	No
rs12189178	5	50914726	T	C	0.038	0.036	0.005	2.2e-15	BMI	Yengo	non-COJO	Yes
rs6449531	5	60712212	A	G	0.354	-0.013	0.002	2.1e-12	BMI	Yengo	non-COJO	No

rs6888159	5	63932234	C	G	0.683	0.011	0.002	5.8e-10	BMI	Yengo	non-COJO	No
rs2367112	5	64168193	T	G	0.508	0.012	0.002	2.3e-13	BMI	Yengo	non-COJO	Yes
rs25832	5	66175682	A	G	0.732	0.012	0.002	9.2e-10	BMI	Yengo	non-COJO	Yes
rs2307111	5	75003678	T	C	0.604	0.026	0.002	1.6e-58	BMI	Yengo	non-COJO	No
rs368863	5	77372852	T	C	0.239	-0.012	0.002	8.1e-09	BMI	Yengo	non-COJO	Yes
rs12514473	5	80818639	T	C	0.769	0.017	0.002	8.8e-17	BMI	Yengo	non-COJO	No
rs7444298	5	87730027	A	G	0.754	0.018	0.002	7.8e-19	BMI	Yengo	non-COJO	Yes
rs2304607	5	87988733	A	G	0.852	-0.032	0.002	1.7e-36	BMI	Yengo	non-COJO	No
rs12655756	5	88858208	A	T	0.370	0.014	0.002	1.9e-14	BMI	Yengo	non-COJO	Yes
rs159032	5	94206202	T	C	0.244	0.013	0.002	1.9e-10	BMI	Yengo	non-COJO	Yes
rs6235	5	95728898	C	G	0.730	-0.018	0.002	1.5e-19	BMI	Yengo	non-COJO	No
rs2611742	5	95856501	T	C	0.596	-0.015	0.002	3.7e-18	BMI	Yengo	non-COJO	Yes
rs3822683	5	96080883	A	G	0.781	0.014	0.002	6.1e-12	BMI	Yengo	non-COJO	Yes
rs156151	6	104799007	C	G	0.191	-0.016	0.002	1.9e-14	BMI	Yengo	non-COJO	Yes
rs3800229	6	108996963	T	G	0.712	0.018	0.002	1.4e-22	BMI	Yengo	non-COJO	No
rs2357760	6	120213880	A	G	0.675	0.014	0.002	6.8e-17	BMI	Yengo	non-COJO	No

rs2228213	6	12124855	A	G	0.348	-0.014	0.002	4.6e-16	BMI	Yengo	non-COJO	Yes
rs2875762	6	124925032	C	G	0.247	0.014	0.002	1.2e-11	BMI	Yengo	non-COJO	No
rs13209968	6	126089285	C	G	0.518	0.011	0.002	3.1e-11	BMI	Yengo	non-COJO	Yes
rs6569648	6	130349119	T	C	0.773	-0.013	0.002	3.7e-11	BMI	Yengo	non-COJO	No
rs9367368	6	13189275	T	C	0.697	0.012	0.002	1e-11	BMI	Yengo	non-COJO	No
rs2781668	6	131897278	T	C	0.161	0.017	0.002	4e-13	BMI	Yengo	non-COJO	Yes
rs13201877	6	137675541	A	G	0.860	-0.015	0.002	2.7e-10	BMI	Yengo	non-COJO	No
rs2185027	6	153381622	A	C	0.703	-0.014	0.002	5e-14	BMI	Yengo	non-COJO	No
rs10499276	6	154309808	T	C	0.124	0.017	0.002	2.2e-12	BMI	Yengo	non-COJO	Yes
rs487060	6	160774459	T	C	0.482	0.011	0.002	1.6e-11	BMI	Yengo	non-COJO	Yes
rs13191362	6	163033350	A	G	0.880	0.024	0.002	5.9e-21	BMI	Yengo	non-COJO	Yes
rs11753081	6	20705590	T	G	0.825	0.014	0.002	8.9e-11	BMI	Yengo	non-COJO	No
rs7760082	6	21919387	A	G	0.665	-0.012	0.002	2.9e-11	BMI	Yengo	non-COJO	No
rs6900723	6	23876240	T	C	0.676	-0.011	0.002	1.4e-09	BMI	Yengo	non-COJO	Yes
rs853679	6	28296863	A	C	0.141	0.013	0.002	2.8e-09	BMI	Yengo	non-COJO	Yes
rs498240	6	31892592	A	G	0.066	-0.027	0.003	1.6e-15	BMI	Yengo	non-COJO	No
rs419261	6	33554147	T	C	0.404	0.011	0.002	1.9e-10	BMI	Yengo	non-COJO	No

rs2814992	6	34617144	A	G	0.660	-0.024	0.002	4.1e-45	BMI	Yengo	non-COJO	Yes
rs12215331	6	34644749	T	C	0.786	0.018	0.002	4.3e-18	BMI	Yengo	non-COJO	Yes
rs6938239	6	34683635	A	G	0.850	-0.027	0.002	2.4e-28	BMI	Yengo	non-COJO	Yes
rs9394312	6	35672330	C	G	0.492	0.011	0.002	2.3e-10	BMI	Yengo	non-COJO	Yes
rs17757975	6	38214150	T	C	0.852	0.014	0.002	4.2e-09	BMI	Yengo	non-COJO	Yes
rs847747	6	40080069	T	G	0.296	-0.011	0.002	2.1e-09	BMI	Yengo	non-COJO	No
rs2033529	6	40348653	A	G	0.706	-0.020	0.002	1.9e-30	BMI	Yengo	non-COJO	Yes
rs7748777	6	41133806	A	G	0.459	0.010	0.002	1.6e-10	BMI	Yengo	non-COJO	Yes
rs9349239	6	42676480	A	G	0.492	0.012	0.002	1.3e-12	BMI	Yengo	non-COJO	No
rs998584	6	43757896	A	C	0.478	-0.013	0.002	1.3e-14	BMI	Yengo	non-COJO	Yes
rs10456637	6	50763935	A	T	0.741	0.013	0.002	4.3e-12	BMI	Yengo	non-COJO	No
rs987237	6	50803050	A	G	0.820	-0.041	0.002	9.3e-84	BMI	Yengo	non-COJO	Yes
rs2635727	6	50820940	T	C	0.254	-0.028	0.002	1.3e-49	BMI	Yengo	non-COJO	Yes
rs1178060	6	50914343	A	G	0.847	0.019	0.002	6.8e-17	BMI	Yengo	non-COJO	Yes
rs2504674	6	51160682	C	G	0.434	-0.011	0.002	1.2e-10	BMI	Yengo	non-COJO	Yes
rs1358808	6	51825285	C	G	0.674	-0.014	0.002	9.2e-15	BMI	Yengo	non-COJO	Yes
rs4278019	6	53693410	A	T	0.282	0.011	0.002	5e-09	BMI	Yengo	non-COJO	No

rs9475173	6	55013291	A	G	0.654	0.011	0.002	6.6e-09	BMI	Yengo	non-COJO	Yes
rs1020548	6	56810539	A	G	0.834	-0.013	0.002	6.6e-09	BMI	Yengo	non-COJO	Yes
rs6921533	6	73742334	T	C	0.288	0.012	0.002	5.6e-10	BMI	Yengo	non-COJO	No
rs9688431	6	73922654	T	C	0.940	0.023	0.004	2.4e-11	BMI	Yengo	non-COJO	Yes
rs9294260	6	83433228	A	G	0.473	0.015	0.002	1.8e-19	BMI	Yengo	non-COJO	No
rs1853639	6	87606842	A	G	0.636	-0.011	0.002	1.2e-09	BMI	Yengo	non-COJO	Yes
rs9362662	6	90296588	A	G	0.480	0.011	0.002	1.2e-10	BMI	Yengo	non-COJO	No
rs1324110	6	93913200	C	G	0.439	-0.010	0.002	6.8e-10	BMI	Yengo	non-COJO	No
rs9463175	6	9510030	T	C	0.348	-0.011	0.002	4.2e-10	BMI	Yengo	non-COJO	No
rs13209872	6	97753223	C	G	0.340	-0.015	0.002	1.4e-16	BMI	Yengo	non-COJO	Yes
rs901630	6	98539519	T	C	0.397	-0.015	0.002	1.9e-18	BMI	Yengo	non-COJO	No
rs11496125	7	103417557	T	C	0.421	0.017	0.002	3e-22	BMI	Yengo	non-COJO	No
rs10953620	7	109173373	A	C	0.517	-0.010	0.002	5.4e-09	BMI	Yengo	non-COJO	Yes
rs13227658	7	113353254	T	C	0.553	-0.016	0.002	1.7e-19	BMI	Yengo	non-COJO	Yes
rs12705987	7	114349212	A	T	0.404	0.014	0.002	9.5e-15	BMI	Yengo	non-COJO	No
rs1899689	7	121964349	T	C	0.399	0.012	0.002	1.5e-12	BMI	Yengo	non-COJO	No

rs2283093	7	126721231	T	C	0.207	0.013	0.002	3.1e-09	BMI	Yengo	non-COJO	No
rs972283	7	130466854	A	G	0.485	0.010	0.002	5.1e-09	BMI	Yengo	non-COJO	Yes
rs3800649	7	137424509	A	G	0.277	0.012	0.002	3.2e-10	BMI	Yengo	non-COJO	No
rs1814170	7	138794149	A	T	0.895	0.020	0.003	2.1e-12	BMI	Yengo	non-COJO	Yes
rs11773362	7	147668180	T	C	0.337	-0.011	0.002	1.5e-09	BMI	Yengo	non-COJO	No
rs4725984	7	150668514	T	C	0.359	-0.013	0.002	1.4e-13	BMI	Yengo	non-COJO	No
rs6968554	7	17287106	A	G	0.360	-0.010	0.002	3.5e-09	BMI	Yengo	non-COJO	No
rs6461115	7	2103668	A	G	0.772	0.014	0.002	1.2e-13	BMI	Yengo	non-COJO	No
rs40245	7	21470536	A	T	0.359	0.011	0.002	1.9e-09	BMI	Yengo	non-COJO	Yes
rs4307239	7	24354300	A	G	0.542	-0.012	0.002	3.9e-11	BMI	Yengo	non-COJO	Yes
rs11971041	7	26698848	A	G	0.906	-0.021	0.003	1e-11	BMI	Yengo	non-COJO	No
rs4722672	7	27231762	T	C	0.815	-0.015	0.002	1.8e-12	BMI	Yengo	non-COJO	Yes
rs849135	7	28196413	A	G	0.491	0.011	0.002	2e-11	BMI	Yengo	non-COJO	No
rs4722398	7	3125220	T	C	0.134	0.016	0.002	3.6e-10	BMI	Yengo	non-COJO	No
rs215632	7	32368524	A	G	0.362	0.015	0.002	3.7e-17	BMI	Yengo	non-COJO	Yes
rs1229057	7	39054538	T	C	0.122	0.017	0.003	2.8e-10	BMI	Yengo	non-COJO	No
rs799449	7	44784697	T	C	0.550	0.013	0.002	8.7e-14	BMI	Yengo	non-COJO	No

rs10269783	7	49616203	A	G	0.390	0.013	0.002	1.4e-15	BMI	Yengo	non-COJO	Yes
rs3807566	7	50564204	T	G	0.443	-0.013	0.002	2e-13	BMI	Yengo	non-COJO	No
rs6463489	7	5542513	T	C	0.109	0.016	0.003	3.1e-09	BMI	Yengo	non-COJO	Yes
rs7784465	7	6418275	T	C	0.861	-0.016	0.002	1.1e-10	BMI	Yengo	non-COJO	Yes
rs1035010	7	69598328	T	C	0.257	0.014	0.002	6.2e-12	BMI	Yengo	non-COJO	No
rs4718966	7	70040558	T	C	0.418	0.013	0.002	4.6e-13	BMI	Yengo	non-COJO	Yes
rs13227433	7	74094721	T	G	0.744	-0.016	0.002	1.4e-14	BMI	Yengo	non-COJO	No
rs17207196	7	75101065	T	C	0.412	-0.022	0.002	2.1e-35	BMI	Yengo	non-COJO	Yes
rs740157	7	77055885	A	G	0.432	0.012	0.002	1.8e-12	BMI	Yengo	non-COJO	No
rs1544459	7	77417584	T	C	0.546	-0.010	0.002	2.2e-10	BMI	Yengo	non-COJO	Yes
rs1852006	7	77829768	A	G	0.352	-0.016	0.002	4.9e-18	BMI	Yengo	non-COJO	Yes
rs7805441	7	78121458	T	C	0.509	0.011	0.002	3.4e-10	BMI	Yengo	non-COJO	Yes
rs6963840	7	78144371	T	C	0.211	0.015	0.002	3.4e-10	BMI	Yengo	non-COJO	Yes
rs13247665	7	93232057	T	C	0.641	-0.014	0.002	1.4e-14	BMI	Yengo	non-COJO	No
rs13240600	7	99064466	A	G	0.845	0.020	0.002	3.5e-17	BMI	Yengo	non-COJO	No
rs3134353	8	101947453	A	T	0.387	-0.012	0.002	2.5e-12	BMI	Yengo	non-COJO	No
rs11250076	8	10647823	A	G	0.438	0.018	0.002	3.2e-23	BMI	Yengo	non-COJO	Yes

rs11783247	8	10788875	T	C	0.538	-0.017	0.002	1.2e-24	BMI	Yengo	non-COJO	Yes
rs3808434	8	116559435	A	G	0.448	0.011	0.002	1.3e-11	BMI	Yengo	non-COJO	No
rs2721965	8	116662038	A	C	0.666	0.017	0.002	1.1e-20	BMI	Yengo	non-COJO	Yes
rs4841659	8	11828200	T	C	0.478	0.015	0.002	9.2e-18	BMI	Yengo	non-COJO	Yes
rs11781699	8	118863061	T	C	0.810	-0.013	0.002	3.1e-10	BMI	Yengo	non-COJO	No
rs12675063	8	132879047	A	T	0.887	-0.016	0.003	1.3e-09	BMI	Yengo	non-COJO	No
rs16906845	8	138215228	A	G	0.067	-0.022	0.004	2.2e-09	BMI	Yengo	non-COJO	Yes
rs13263601	8	14095900	A	C	0.652	-0.015	0.002	2.2e-17	BMI	Yengo	non-COJO	No
rs903959	8	142630782	A	T	0.396	0.011	0.002	1.6e-09	BMI	Yengo	non-COJO	Yes
rs10110727	8	14324437	A	G	0.293	0.014	0.002	3.2e-11	BMI	Yengo	non-COJO	Yes
rs2543132	8	15536311	C	G	0.813	0.015	0.002	5e-11	BMI	Yengo	non-COJO	Yes
rs4366093	8	20639811	T	C	0.320	-0.012	0.002	6.7e-11	BMI	Yengo	non-COJO	No
rs11781222	8	23389571	T	C	0.871	0.016	0.002	5.3e-11	BMI	Yengo	non-COJO	Yes
rs17446091	8	27167942	T	C	0.793	-0.012	0.002	1.8e-09	BMI	Yengo	non-COJO	Yes
rs1982441	8	28021769	T	G	0.138	0.018	0.003	7e-12	BMI	Yengo	non-COJO	Yes
rs2100814	8	28118130	A	G	0.410	0.011	0.002	1.2e-10	BMI	Yengo	non-COJO	No

rs1362910	8	30856464	A	G	0.418	0.012	0.002	1.2e-12	BMI	Yengo	non-COJO	Yes
rs7844647	8	34503776	T	C	0.732	0.012	0.002	2.8e-11	BMI	Yengo	non-COJO	No
rs1658820	8	4288577	T	G	0.247	0.014	0.002	5.9e-12	BMI	Yengo	non-COJO	No
rs4737183	8	64720693	A	G	0.530	0.011	0.002	1.1e-10	BMI	Yengo	non-COJO	No
rs16932761	8	67202787	A	G	0.254	-0.014	0.002	1.7e-12	BMI	Yengo	non-COJO	Yes
rs1431659	8	73439070	A	G	0.266	0.020	0.002	6e-24	BMI	Yengo	non-COJO	Yes
rs2170382	8	74689288	T	C	0.120	0.017	0.003	2.4e-10	BMI	Yengo	non-COJO	No
rs1405348	8	77228222	A	G	0.432	-0.020	0.002	6.2e-32	BMI	Yengo	non-COJO	Yes
rs16907751	8	81375457	T	C	0.105	-0.021	0.003	1.6e-12	BMI	Yengo	non-COJO	No
rs7827182	8	8380471	C	G	0.495	0.018	0.002	1.7e-22	BMI	Yengo	non-COJO	No
rs733594	8	85077686	T	C	0.718	0.014	0.002	5.9e-14	BMI	Yengo	non-COJO	Yes
rs2634047	8	85696337	C	G	0.242	-0.015	0.002	2.5e-13	BMI	Yengo	non-COJO	No
rs7006629	8	87519542	T	C	0.526	0.011	0.002	2.5e-10	BMI	Yengo	non-COJO	Yes
rs1700137	8	89461609	T	C	0.312	-0.012	0.002	2.5e-10	BMI	Yengo	non-COJO	Yes
rs1394	8	9511654	A	G	0.640	-0.015	0.002	2.8e-19	BMI	Yengo	non-COJO	Yes
rs12680842	8	95582606	A	G	0.680	0.013	0.002	4.4e-14	BMI	Yengo	non-COJO	Yes
rs450231	9	101481205	A	G	0.753	-0.013	0.002	2.1e-10	BMI	Yengo	non-COJO	No

rs10118701	9	103061366	A	G	0.677	-0.016	0.002	1.1e-18	BMI	Yengo	non-COJO	Yes
rs10989568	9	104396304	A	G	0.462	0.011	0.002	6.6e-10	BMI	Yengo	non-COJO	Yes
rs7024334	9	109072075	T	G	0.226	0.014	0.002	3.1e-12	BMI	Yengo	non-COJO	Yes
rs6477694	9	111932342	T	C	0.644	-0.012	0.002	3.8e-13	BMI	Yengo	non-COJO	No
rs17820822	9	11831420	T	G	0.645	0.014	0.002	2.9e-15	BMI	Yengo	non-COJO	No
rs1928295	9	120378483	T	C	0.554	0.014	0.002	5.4e-18	BMI	Yengo	non-COJO	No
rs7865157	9	122631560	T	C	0.107	0.018	0.003	3.7e-10	BMI	Yengo	non-COJO	Yes
rs10818810	9	126096522	A	G	0.391	0.013	0.002	1.1e-13	BMI	Yengo	non-COJO	Yes
rs10818938	9	127049237	A	G	0.422	0.011	0.002	5.1e-11	BMI	Yengo	non-COJO	Yes
rs3829849	9	129390800	T	C	0.359	0.010	0.002	5.9e-09	BMI	Yengo	non-COJO	No
rs3902840	9	129419025	A	G	0.086	0.022	0.003	3.2e-13	BMI	Yengo	non-COJO	Yes
rs13292976	9	129467340	T	C	0.446	0.013	0.002	3.1e-14	BMI	Yengo	non-COJO	No
rs7871866	9	131027982	C	G	0.153	0.019	0.002	2.3e-14	BMI	Yengo	non-COJO	Yes
rs4740383	9	133783566	A	G	0.416	0.013	0.002	1.9e-12	BMI	Yengo	non-COJO	Yes
rs11792069	9	140646121	A	G	0.830	0.014	0.002	6.5e-10	BMI	Yengo	non-COJO	No
rs11790280	9	14651283	T	C	0.614	-0.010	0.002	7.1e-09	BMI	Yengo	non-COJO	Yes
rs6474945	9	15670492	T	G	0.450	-0.019	0.002	4.7e-30	BMI	Yengo	non-COJO	Yes

rs10962549	9	16719445	T	C	0.168	0.020	0.002	2.5e-17	BMI	Yengo	non-COJO	Yes
rs7874154	9	27777012	T	C	0.502	-0.013	0.002	1.8e-13	BMI	Yengo	non-COJO	No
rs1412235	9	28410996	C	G	0.318	0.025	0.002	6e-45	BMI	Yengo	non-COJO	Yes
rs10971712	9	33820938	T	C	0.108	-0.020	0.003	6.4e-13	BMI	Yengo	non-COJO	No
rs13290794	9	37183628	A	G	0.358	-0.014	0.002	1.9e-15	BMI	Yengo	non-COJO	Yes
rs7042372	9	6959840	A	G	0.657	0.012	0.002	3.8e-11	BMI	Yengo	non-COJO	No
rs2174307	9	73791849	C	G	0.407	0.012	0.002	4.9e-12	BMI	Yengo	non-COJO	No
rs10867256	9	81367391	T	C	0.553	-0.012	0.002	8.7e-12	BMI	Yengo	non-COJO	No
rs1865341	9	8845911	T	C	0.758	0.013	0.002	2.5e-10	BMI	Yengo	non-COJO	No
rs3739733	9	88897891	A	G	0.780	0.013	0.002	5.3e-10	BMI	Yengo	non-COJO	Yes
rs10797115	9	92191256	T	C	0.536	0.012	0.002	9.9e-13	BMI	Yengo	non-COJO	No
rs7869771	9	94180627	A	C	0.735	0.014	0.002	4.9e-13	BMI	Yengo	non-COJO	Yes
rs4744275	9	96482633	A	G	0.266	0.014	0.002	7e-15	BMI	Yengo	non-COJO	No
rs1983864	10	100017453	T	G	0.667	0.016	0.002	3.7e-18	BMI	Yengo	non-COJO	Yes
rs17094222	10	102395440	T	C	0.796	-0.018	0.002	2.2e-19	BMI	Yengo	non-COJO	Yes
rs10883553	10	102635475	A	C	0.451	0.012	0.002	1.9e-11	BMI	Yengo	non-COJO	No

rs9787495	10	103206115	A	G	0.437	-0.010	0.002	3.1e-09	BMI	Yengo	non-COJO	Yes
rs7083450	10	103984060	T	C	0.839	0.016	0.002	1.7e-12	BMI	Yengo	non-COJO	Yes
rs10883759	10	104412049	A	G	0.302	-0.012	0.002	5.4e-12	BMI	Yengo	non-COJO	Yes
rs12411886	10	104685299	A	C	0.083	0.027	0.003	1.5e-19	BMI	Yengo	non-COJO	Yes
rs7903146	10	114758349	T	C	0.291	-0.018	0.002	1.3e-23	BMI	Yengo	non-COJO	No
rs10886017	10	118672531	A	C	0.252	0.015	0.002	1.4e-15	BMI	Yengo	non-COJO	Yes
rs845084	10	125220036	A	G	0.268	0.014	0.002	1.3e-12	BMI	Yengo	non-COJO	No
rs17636031	10	126594078	T	C	0.730	-0.016	0.002	1.2e-17	BMI	Yengo	non-COJO	No
rs7893571	10	16750129	T	G	0.662	0.014	0.002	1.8e-13	BMI	Yengo	non-COJO	No
rs12776880	10	19776828	A	T	0.683	0.013	0.002	3e-11	BMI	Yengo	non-COJO	No
rs7084454	10	21821274	A	G	0.335	0.019	0.002	4e-25	BMI	Yengo	non-COJO	Yes
rs11251352	10	2585792	A	G	0.401	-0.011	0.002	7e-10	BMI	Yengo	non-COJO	No
rs3781099	10	27318776	T	C	0.082	0.021	0.003	2.5e-11	BMI	Yengo	non-COJO	Yes
rs3851083	10	33862727	A	G	0.432	-0.010	0.002	4.1e-10	BMI	Yengo	non-COJO	No
rs1937684	10	53680085	A	T	0.659	0.011	0.002	8.7e-10	BMI	Yengo	non-COJO	No
rs2163188	10	65314711	C	G	0.474	0.013	0.002	2e-14	BMI	Yengo	non-COJO	No
rs12098284	10	76047464	T	C	0.124	0.018	0.003	1.8e-11	BMI	Yengo	non-COJO	No

rs7899106	10	87410904	A	G	0.952	-0.033	0.004	1e-18	BMI	Yengo	non-COJO	No
rs10887578	10	88096047	C	G	0.490	0.013	0.002	1.6e-13	BMI	Yengo	non-COJO	No
rs2631681	10	93032943	T	C	0.325	-0.011	0.002	8.9e-11	BMI	Yengo	non-COJO	Yes
rs577525	10	99769388	T	C	0.432	-0.017	0.002	9.7e-22	BMI	Yengo	non-COJO	No
rs719802	11	113234679	T	C	0.380	0.010	0.002	9.5e-09	BMI	Yengo	non-COJO	No
rs1048932	11	115044850	A	C	0.416	-0.016	0.002	3.8e-22	BMI	Yengo	non-COJO	No
rs12420725	11	117017530	A	G	0.941	-0.023	0.004	1.3e-09	BMI	Yengo	non-COJO	Yes
rs1037587	11	11796727	T	C	0.454	0.011	0.002	1.1e-09	BMI	Yengo	non-COJO	No
rs9332817	11	118365210	C	G	0.026	-0.038	0.006	1.7e-10	BMI	Yengo	non-COJO	Yes
rs1003081	11	118913993	T	C	0.450	0.012	0.002	1.3e-13	BMI	Yengo	non-COJO	Yes
rs4936671	11	121942512	C	G	0.367	0.010	0.002	6.2e-09	BMI	Yengo	non-COJO	Yes
rs7941030	11	122522375	T	C	0.614	-0.011	0.002	2e-11	BMI	Yengo	non-COJO	No
rs3134438	11	122765667	A	C	0.286	0.011	0.002	6.1e-09	BMI	Yengo	non-COJO	Yes
rs1625427	11	131957293	T	C	0.650	0.013	0.002	1.4e-12	BMI	Yengo	non-COJO	Yes
rs4936175	11	132641959	T	C	0.556	-0.012	0.002	1.4e-12	BMI	Yengo	non-COJO	No
rs900144	11	13294268	T	C	0.567	0.017	0.002	8.7e-22	BMI	Yengo	non-COJO	No
rs329651	11	133767622	T	G	0.806	0.016	0.002	9e-15	BMI	Yengo	non-COJO	No

rs12364470	11	134601012	T	G	0.837	-0.018	0.002	1.1e-15	BMI	Yengo	non-COJO	No
rs10832778	11	17394073	C	G	0.378	-0.012	0.002	1.3e-13	BMI	Yengo	non-COJO	Yes
rs10840606	11	2234690	A	G	0.826	-0.016	0.002	3.2e-12	BMI	Yengo	non-COJO	No
rs7124442	11	27677041	T	C	0.683	-0.029	0.002	4.6e-61	BMI	Yengo	non-COJO	No
rs6265	11	27679916	T	C	0.195	-0.041	0.002	1e-86	BMI	Yengo	non-COJO	Yes
rs7948120	11	28763321	T	C	0.260	-0.013	0.002	7.3e-12	BMI	Yengo	non-COJO	No
rs1552717	11	29158495	A	T	0.865	0.015	0.002	3.5e-09	BMI	Yengo	non-COJO	Yes
rs1782507	11	30243868	T	G	0.653	-0.014	0.002	1.3e-13	BMI	Yengo	non-COJO	No
rs223051	11	32131303	T	C	0.676	0.011	0.002	1.1e-09	BMI	Yengo	non-COJO	Yes
rs10838122	11	43551416	T	C	0.480	-0.010	0.002	1.5e-09	BMI	Yengo	non-COJO	No
rs12577642	11	43728534	A	T	0.686	-0.021	0.002	9.9e-31	BMI	Yengo	non-COJO	Yes
rs12574668	11	46422686	A	C	0.178	0.013	0.002	8.8e-09	BMI	Yengo	non-COJO	Yes
rs7124681	11	47529947	A	C	0.413	0.026	0.002	3.2e-58	BMI	Yengo	non-COJO	Yes
rs7131262	11	47836302	A	T	0.260	-0.022	0.002	1e-32	BMI	Yengo	non-COJO	Yes
rs7120873	11	49459474	T	C	0.111	0.017	0.003	3.4e-10	BMI	Yengo	non-COJO	No
rs11600990	11	64082807	T	C	0.157	-0.018	0.002	3.8e-14	BMI	Yengo	non-COJO	No

rs7102454	11	65594820	T	C	0.656	-0.016	0.002	2.4e-18	BMI	Yengo	non-COJO	No
rs587230	11	69299771	A	G	0.165	0.015	0.002	4.7e-11	BMI	Yengo	non-COJO	No
rs1789165	11	69481969	A	G	0.639	0.014	0.002	8e-16	BMI	Yengo	non-COJO	Yes
rs7123876	11	72444583	T	C	0.754	-0.012	0.002	2.2e-10	BMI	Yengo	non-COJO	Yes
rs7117238	11	78040259	A	G	0.168	-0.013	0.002	2.5e-09	BMI	Yengo	non-COJO	Yes
rs12575252	11	8694073	C	G	0.351	-0.018	0.002	1.8e-26	BMI	Yengo	non-COJO	Yes
rs10830452	11	89966202	A	G	0.671	-0.011	0.002	2.1e-09	BMI	Yengo	non-COJO	No
rs2605603	11	93221105	A	G	0.489	-0.010	0.002	2.5e-10	BMI	Yengo	non-COJO	No
rs4764949	12	103658096	A	G	0.664	0.018	0.002	1.7e-23	BMI	Yengo	non-COJO	Yes
rs11611496	12	108413828	A	G	0.222	-0.017	0.002	1.7e-16	BMI	Yengo	non-COJO	No
rs17608150	12	110046698	T	C	0.075	0.020	0.003	1.3e-10	BMI	Yengo	non-COJO	Yes
rs6606686	12	110903380	C	G	0.690	-0.014	0.002	7.6e-15	BMI	Yengo	non-COJO	Yes
rs11066301	12	112871372	A	G	0.566	0.011	0.002	4.4e-12	BMI	Yengo	non-COJO	Yes
rs4766710	12	114437708	A	G	0.936	0.023	0.004	3.7e-11	BMI	Yengo	non-COJO	No
rs7973955	12	118409640	A	G	0.285	-0.013	0.002	3.7e-11	BMI	Yengo	non-COJO	Yes
rs3887080	12	121661966	A	G	0.121	0.018	0.003	5.1e-12	BMI	Yengo	non-COJO	Yes
rs7133378	12	124409502	A	G	0.327	0.012	0.002	9.4e-13	BMI	Yengo	non-COJO	Yes

rs10773049	12	124506631	T	C	0.598	-0.012	0.002	4.1e-12	BMI	Yengo	non-COJO	No
rs7968230	12	133481917	A	G	0.323	0.013	0.002	1.6e-12	BMI	Yengo	non-COJO	No
rs12422552	12	14413931	C	G	0.266	-0.013	0.002	1.6e-11	BMI	Yengo	non-COJO	No
rs10744146	12	17212881	A	G	0.515	-0.012	0.002	1.4e-12	BMI	Yengo	non-COJO	No
rs621042	12	18789007	A	C	0.451	-0.011	0.002	6.3e-10	BMI	Yengo	non-COJO	Yes
rs2429150	12	2152655	A	C	0.584	-0.011	0.002	2.7e-10	BMI	Yengo	non-COJO	No
rs10842240	12	24060075	C	G	0.116	0.022	0.003	3.1e-16	BMI	Yengo	non-COJO	Yes
rs10772055	12	33379440	C	G	0.866	-0.017	0.002	2.1e-12	BMI	Yengo	non-COJO	No
rs10876418	12	39428802	T	C	0.232	-0.012	0.002	2.8e-10	BMI	Yengo	non-COJO	Yes
rs2733287	12	41880909	A	C	0.517	-0.016	0.002	6.8e-20	BMI	Yengo	non-COJO	Yes
rs7138803	12	50247468	A	G	0.377	0.030	0.002	2.3e-71	BMI	Yengo	non-COJO	No
rs4077093	12	51593616	T	G	0.217	0.013	0.002	5.1e-09	BMI	Yengo	non-COJO	Yes
rs4759073	12	54653258	A	G	0.400	-0.012	0.002	2.8e-11	BMI	Yengo	non-COJO	Yes
rs4759228	12	56508409	C	G	0.297	-0.016	0.002	5.9e-16	BMI	Yengo	non-COJO	Yes
rs7975187	12	60964108	A	G	0.793	-0.013	0.002	1.4e-09	BMI	Yengo	non-COJO	No
rs1819844	12	68205604	A	G	0.180	0.014	0.002	2.6e-11	BMI	Yengo	non-COJO	Yes
rs10878946	12	69642315	T	C	0.714	-0.014	0.002	3.6e-13	BMI	Yengo	non-COJO	No

rs11115176	12	82465797	T	C	0.760	0.012	0.002	2e-10	BMI	Yengo	non-COJO	No
rs2731222	12	90595383	A	C	0.270	0.013	0.002	1.5e-11	BMI	Yengo	non-COJO	Yes
rs11611246	12	939480	T	G	0.210	0.024	0.002	5e-32	BMI	Yengo	non-COJO	No
rs10745785	12	97586257	T	C	0.667	-0.011	0.002	1.2e-09	BMI	Yengo	non-COJO	No
rs651548	12	99560183	A	G	0.368	0.014	0.002	2e-14	BMI	Yengo	non-COJO	No
rs2479958	13	111984244	A	G	0.492	0.015	0.002	1.5e-17	BMI	Yengo	non-COJO	No
rs1218822	13	28011963	A	G	0.666	0.017	0.002	1.9e-22	BMI	Yengo	non-COJO	No
rs1006353	13	28047269	A	G	0.248	0.013	0.002	2.3e-11	BMI	Yengo	non-COJO	Yes
rs9507983	13	28620036	T	C	0.607	-0.016	0.002	1.4e-18	BMI	Yengo	non-COJO	Yes
rs1045411	13	31033232	T	C	0.265	-0.015	0.002	2.3e-15	BMI	Yengo	non-COJO	No
rs9595908	13	33184288	T	C	0.628	0.016	0.002	4.2e-21	BMI	Yengo	non-COJO	Yes
rs9603697	13	40783323	T	C	0.319	0.014	0.002	2.6e-14	BMI	Yengo	non-COJO	No
rs12429545	13	54102206	A	G	0.125	0.032	0.002	9.6e-38	BMI	Yengo	non-COJO	No
rs9527706	13	58402479	A	G	0.729	-0.012	0.002	5.1e-10	BMI	Yengo	non-COJO	No
rs9538141	13	59178258	A	G	0.509	0.016	0.002	3.5e-21	BMI	Yengo	non-COJO	Yes
rs1333423	13	59425111	A	T	0.225	0.017	0.002	2.1e-16	BMI	Yengo	non-COJO	Yes

rs892261	13	65884191	T	C	0.443	-0.010	0.002	2.2e-09	BMI	Yengo	non-COJO	Yes
rs9540493	13	66205704	A	G	0.442	0.014	0.002	8.1e-17	BMI	Yengo	non-COJO	Yes
rs9571687	13	67472713	A	C	0.329	-0.013	0.002	2.8e-12	BMI	Yengo	non-COJO	No
rs629443	13	76386075	T	G	0.250	0.012	0.002	1.4e-09	BMI	Yengo	non-COJO	Yes
rs1668633	13	78371890	T	C	0.574	0.010	0.002	8.7e-09	BMI	Yengo	non-COJO	No
rs9530843	13	79563749	A	C	0.556	0.013	0.002	4.8e-13	BMI	Yengo	non-COJO	No
rs1927790	13	96922191	T	C	0.589	-0.015	0.002	1.8e-19	BMI	Yengo	non-COJO	No
rs7334078	13	99120484	T	C	0.712	0.012	0.002	2.2e-10	BMI	Yengo	non-COJO	No
rs12147845	14	101144596	T	C	0.114	0.020	0.003	4.5e-13	BMI	Yengo	non-COJO	Yes
rs7147503	14	101539384	T	C	0.370	-0.012	0.002	2e-11	BMI	Yengo	non-COJO	Yes
rs8016771	14	102649451	T	G	0.912	-0.019	0.003	1.1e-09	BMI	Yengo	non-COJO	Yes
rs3803286	14	103246470	A	G	0.343	0.018	0.002	4.1e-23	BMI	Yengo	non-COJO	Yes
rs2010281	14	103862322	A	G	0.355	-0.016	0.002	6.7e-21	BMI	Yengo	non-COJO	No
rs10132280	14	25928179	A	C	0.302	-0.022	0.002	5.6e-35	BMI	Yengo	non-COJO	No
rs4981693	14	29680331	A	G	0.771	0.021	0.002	6.9e-24	BMI	Yengo	non-COJO	No
rs12885454	14	29736838	A	C	0.343	-0.018	0.002	2.4e-27	BMI	Yengo	non-COJO	Yes
rs8016859	14	30484722	C	G	0.040	0.035	0.004	7.1e-16	BMI	Yengo	non-COJO	Yes

rs17522122	14	33302882	T	G	0.481	0.016	0.002	1.5e-21	BMI	Yengo	non-COJO	Yes
rs9806058	14	35673470	A	T	0.877	0.016	0.003	4e-10	BMI	Yengo	non-COJO	Yes
rs1956151	14	40101060	A	G	0.821	-0.013	0.002	7.3e-09	BMI	Yengo	non-COJO	No
rs12587412	14	47272423	T	G	0.490	0.015	0.002	4.8e-17	BMI	Yengo	non-COJO	Yes
rs217671	14	62360464	A	G	0.728	-0.014	0.002	1.3e-13	BMI	Yengo	non-COJO	No
rs3902951	14	69789755	T	G	0.754	-0.013	0.002	7e-12	BMI	Yengo	non-COJO	No
rs17105272	14	77529783	T	C	0.319	0.011	0.002	3.2e-09	BMI	Yengo	non-COJO	No
rs10146527	14	79499850	T	C	0.636	0.014	0.002	2.3e-15	BMI	Yengo	non-COJO	Yes
rs7144011	14	79940383	T	G	0.214	0.028	0.002	5.2e-47	BMI	Yengo	non-COJO	Yes
rs12888545	14	88308044	A	G	0.748	-0.014	0.002	9.1e-12	BMI	Yengo	non-COJO	No
rs1951455	14	91512339	T	C	0.275	-0.014	0.002	4.5e-14	BMI	Yengo	non-COJO	No
rs3850422	14	99671788	A	G	0.446	-0.011	0.002	3.7e-12	BMI	Yengo	non-COJO	No
rs4906908	15	27040082	T	G	0.475	-0.010	0.002	2.5e-09	BMI	Yengo	non-COJO	No
rs4284600	15	31843528	T	C	0.529	-0.012	0.002	1.3e-11	BMI	Yengo	non-COJO	No
rs7181610	15	35826859	A	T	0.858	0.014	0.002	7.8e-09	BMI	Yengo	non-COJO	Yes
rs8036040	15	36402716	A	C	0.493	0.011	0.002	2.7e-10	BMI	Yengo	non-COJO	No
rs12439798	15	46584787	T	G	0.423	0.012	0.002	6.9e-13	BMI	Yengo	non-COJO	No

rs3736485	15	51748610	A	G	0.456	0.013	0.002	2.5e-16	BMI	Yengo	non-COJO	Yes
rs340025	15	60908307	T	C	0.428	-0.012	0.002	1e-13	BMI	Yengo	non-COJO	No
rs8033510	15	61445514	T	C	0.371	0.011	0.002	5.1e-09	BMI	Yengo	non-COJO	No
rs17238110	15	62150364	A	G	0.837	0.035	0.005	2e-12	BMI	Yengo	non-COJO	Yes
rs12595158	15	62316035	T	C	0.024	-0.039	0.005	1.9e-13	BMI	Yengo	non-COJO	Yes
rs11635675	15	63793238	T	G	0.646	0.012	0.002	1.3e-11	BMI	Yengo	non-COJO	No
rs11629783	15	66741387	C	G	0.769	0.015	0.002	9.8e-13	BMI	Yengo	non-COJO	Yes
rs13329567	15	68104367	T	C	0.231	-0.029	0.002	1e-50	BMI	Yengo	non-COJO	Yes
rs7164727	15	73093991	T	C	0.681	0.018	0.002	3.3e-25	BMI	Yengo	non-COJO	Yes
rs11855853	15	78012618	T	C	0.265	-0.014	0.002	2.4e-13	BMI	Yengo	non-COJO	No
rs12595749	15	79432359	A	G	0.571	0.014	0.002	5.7e-16	BMI	Yengo	non-COJO	No
rs12593036	15	81058652	A	G	0.701	0.015	0.002	3.8e-16	BMI	Yengo	non-COJO	Yes
rs12101393	15	92570921	C	G	0.780	0.013	0.002	1.5e-09	BMI	Yengo	non-COJO	No
rs7181498	15	95271404	T	C	0.369	0.016	0.002	1e-19	BMI	Yengo	non-COJO	Yes
rs4985155	16	15129459	A	G	0.663	0.012	0.002	3e-12	BMI	Yengo	non-COJO	No
rs12446632	16	19935389	A	G	0.142	-0.035	0.002	2.9e-50	BMI	Yengo	non-COJO	Yes

rs868554	16	20050466	C	G	0.754	-0.019	0.002	1.2e-20	BMI	Yengo	non-COJO	Yes
rs11074446	16	20255123	T	C	0.869	0.022	0.002	1.8e-20	BMI	Yengo	non-COJO	No
rs9931967	16	20375351	T	G	0.508	0.016	0.002	1e-20	BMI	Yengo	non-COJO	Yes
rs2516739	16	2097158	A	G	0.217	-0.016	0.002	1.4e-14	BMI	Yengo	non-COJO	No
rs9927848	16	23833071	A	C	0.733	-0.012	0.002	6.4e-10	BMI	Yengo	non-COJO	Yes
rs7195386	16	24578458	T	C	0.501	0.013	0.002	1.1e-14	BMI	Yengo	non-COJO	Yes
rs1862451	16	24803620	A	G	0.731	0.014	0.002	1.9e-12	BMI	Yengo	non-COJO	No
rs7187776	16	28857645	A	G	0.593	-0.026	0.002	1.4e-58	BMI	Yengo	non-COJO	Yes
rs1057452	16	29833714	A	G	0.037	0.017	0.002	1.6e-12	BMI	Yengo	non-COJO	No
rs3814883	16	29994922	T	C	0.476	0.023	0.002	1.1e-40	BMI	Yengo	non-COJO	Yes
rs1549293	16	31141993	T	C	0.360	-0.020	0.002	7.6e-33	BMI	Yengo	non-COJO	Yes
rs12448257	16	3599655	A	G	0.218	0.018	0.002	8.1e-20	BMI	Yengo	non-COJO	Yes
rs11866815	16	387867	T	C	0.246	-0.016	0.002	1e-16	BMI	Yengo	non-COJO	No
rs879620	16	4015729	T	C	0.618	0.023	0.002	5.3e-38	BMI	Yengo	non-COJO	Yes
rs2080454	16	49062590	A	C	0.621	-0.013	0.002	1.7e-14	BMI	Yengo	non-COJO	No
rs8047395	16	53798523	A	G	0.506	0.064	0.002	0	BMI	Yengo	non-COJO	No
rs11075986	16	53805344	C	G	0.915	0.032	0.003	5.6e-26	BMI	Yengo	non-COJO	Yes

rs3751813	16	53818708	T	G	0.541	0.060	0.002	2.2e-295	BMI	Yengo	non-COJO	Yes
rs9922708	16	53831146	T	C	0.432	0.069	0.002	0	BMI	Yengo	non-COJO	Yes
rs2075205	16	54153099	A	T	0.587	0.011	0.002	1.8e-10	BMI	Yengo	non-COJO	No
rs12448738	16	56489343	A	C	0.863	-0.017	0.002	2.8e-11	BMI	Yengo	non-COJO	No
rs11075489	16	62803841	T	C	0.483	-0.011	0.002	1.3e-10	BMI	Yengo	non-COJO	Yes
rs10083803	16	6701400	T	C	0.260	-0.013	0.002	5.9e-11	BMI	Yengo	non-COJO	Yes
rs7200919	16	67316600	A	G	0.413	0.010	0.002	9.3e-09	BMI	Yengo	non-COJO	No
rs2307022	16	68381978	A	G	0.334	0.014	0.002	5.5e-15	BMI	Yengo	non-COJO	Yes
rs889398	16	69556715	T	C	0.425	-0.020	0.002	1.3e-32	BMI	Yengo	non-COJO	Yes
rs7919	16	70514828	A	C	0.450	-0.016	0.002	1e-19	BMI	Yengo	non-COJO	Yes
rs11642001	16	71899586	A	G	0.212	-0.014	0.002	5.1e-11	BMI	Yengo	non-COJO	No
rs756717	16	72996162	A	G	0.397	-0.015	0.002	5.4e-18	BMI	Yengo	non-COJO	Yes
rs825680	16	73606563	A	T	0.583	0.010	0.002	6.7e-09	BMI	Yengo	non-COJO	Yes
rs6564360	16	76779612	A	G	0.810	-0.014	0.002	1.2e-09	BMI	Yengo	non-COJO	Yes
rs12922346	16	82438337	C	G	0.266	0.014	0.002	1e-11	BMI	Yengo	non-COJO	No
rs4783241	16	82650384	C	G	0.494	-0.011	0.002	4e-10	BMI	Yengo	non-COJO	Yes
rs7206608	16	82872628	C	G	0.685	-0.013	0.002	1.3e-12	BMI	Yengo	non-COJO	No

rs977540	16	9724750	A	G	0.762	0.014	0.002	2.5e-13	BMI	Yengo	non-COJO	Yes
rs1075901	17	15943910	T	C	0.436	-0.012	0.002	1.2e-13	BMI	Yengo	non-COJO	Yes
rs4516268	17	1846831	A	C	0.192	-0.022	0.002	5.2e-25	BMI	Yengo	non-COJO	No
rs4986044	17	21261560	T	C	0.469	-0.016	0.002	3.3e-23	BMI	Yengo	non-COJO	No
rs7217226	17	2136065	T	G	0.640	-0.013	0.002	2.6e-14	BMI	Yengo	non-COJO	Yes
rs1038088	17	28074563	T	G	0.492	-0.012	0.002	4.6e-13	BMI	Yengo	non-COJO	Yes
rs7211567	17	31460899	T	C	0.220	-0.014	0.002	4.5e-12	BMI	Yengo	non-COJO	No
rs1106908	17	34942595	A	G	0.441	-0.016	0.002	3.1e-22	BMI	Yengo	non-COJO	No
rs4796243	17	35057883	A	G	0.303	-0.012	0.002	6.1e-11	BMI	Yengo	non-COJO	No
rs8070454	17	38160754	T	C	0.387	-0.010	0.002	4.2e-09	BMI	Yengo	non-COJO	Yes
rs16966801	17	39573713	A	G	0.798	-0.016	0.002	1.1e-12	BMI	Yengo	non-COJO	Yes
rs886444	17	46051911	A	G	0.396	-0.010	0.002	8.4e-10	BMI	Yengo	non-COJO	No
rs208015	17	46252346	T	C	0.078	0.036	0.003	1.4e-25	BMI	Yengo	non-COJO	Yes
rs9299	17	46669430	T	C	0.647	0.012	0.002	3.6e-11	BMI	Yengo	non-COJO	Yes
rs11079849	17	47090785	T	C	0.320	-0.019	0.002	4.8e-24	BMI	Yengo	non-COJO	Yes
rs1000940	17	5283252	A	G	0.701	-0.015	0.002	1.1e-17	BMI	Yengo	non-COJO	Yes

rs8071182	17	55336155	A	G	0.174	0.013	0.002	2.1e-09	BMI	Yengo	non-COJO	Yes
rs8075273	17	61728881	A	C	0.282	-0.013	0.002	3.7e-13	BMI	Yengo	non-COJO	No
rs12602912	17	65870073	T	C	0.205	0.018	0.002	9.9e-18	BMI	Yengo	non-COJO	Yes
rs2619976	17	71754545	T	C	0.413	0.010	0.002	6.3e-09	BMI	Yengo	non-COJO	No
rs7209235	17	73759552	A	G	0.695	-0.011	0.002	8e-09	BMI	Yengo	non-COJO	No
rs8081039	17	75995829	T	C	0.057	0.023	0.004	6.1e-10	BMI	Yengo	non-COJO	No
rs1285245	17	77796889	C	G	0.367	-0.012	0.002	1.7e-11	BMI	Yengo	non-COJO	Yes
rs12939549	17	78611724	A	G	0.566	0.018	0.002	2.7e-28	BMI	Yengo	non-COJO	Yes
rs4889782	17	78640510	T	C	0.602	-0.015	0.002	6.6e-17	BMI	Yengo	non-COJO	Yes
rs4969387	17	79081724	C	G	0.746	-0.014	0.002	4.3e-13	BMI	Yengo	non-COJO	Yes
rs9905991	17	80052073	A	G	0.448	0.010	0.002	8.3e-09	BMI	Yengo	non-COJO	Yes
rs17681708	17	9792872	T	C	0.688	-0.011	0.002	7.2e-09	BMI	Yengo	non-COJO	No
rs8097544	18	1839564	A	G	0.848	-0.020	0.002	9.3e-16	BMI	Yengo	non-COJO	Yes
rs12964689	18	21116998	A	G	0.518	0.020	0.002	5.1e-32	BMI	Yengo	non-COJO	No
rs1941697	18	31251276	A	G	0.454	0.012	0.002	1.2e-12	BMI	Yengo	non-COJO	No
rs1365466	18	36182440	T	C	0.741	-0.014	0.002	3.3e-13	BMI	Yengo	non-COJO	Yes
rs555267	18	40992698	T	G	0.330	0.013	0.002	6e-13	BMI	Yengo	non-COJO	Yes

rs954018	18	42598463	A	G	0.305	-0.013	0.002	2.1e-13	BMI	Yengo	non-COJO	No
rs10438964	18	42950629	T	C	0.276	-0.013	0.002	7.6e-11	BMI	Yengo	non-COJO	Yes
rs7239114	18	45921214	A	G	0.540	0.012	0.002	1.2e-13	BMI	Yengo	non-COJO	Yes
rs8092503	18	52479487	A	G	0.768	-0.016	0.002	2.3e-17	BMI	Yengo	non-COJO	Yes
rs11659764	18	53335512	A	T	0.053	-0.025	0.004	8.9e-11	BMI	Yengo	non-COJO	No
rs7243357	18	56883319	T	G	0.827	0.019	0.002	9.1e-20	BMI	Yengo	non-COJO	No
rs2000746	18	57677294	A	G	0.734	0.018	0.002	7e-19	BMI	Yengo	non-COJO	Yes
rs1942866	18	57741783	C	G	0.624	-0.031	0.002	2e-75	BMI	Yengo	non-COJO	Yes
rs8095404	18	57804346	A	T	0.544	-0.026	0.002	1.1e-54	BMI	Yengo	non-COJO	Yes
rs663129	18	57838401	A	G	0.230	0.054	0.002	1.6e-178	BMI	Yengo	non-COJO	Yes
rs8094523	18	57878155	A	G	0.080	-0.030	0.003	4.7e-22	BMI	Yengo	non-COJO	Yes
rs9675376	18	57969244	A	G	0.288	0.035	0.002	2.7e-82	BMI	Yengo	non-COJO	Yes
rs2229616	18	58039276	T	C	0.020	-0.106	0.006	4.7e-71	BMI	Yengo	non-COJO	Yes
rs9951893	18	60739250	T	C	0.525	-0.012	0.002	3.3e-11	BMI	Yengo	non-COJO	No
rs2012927	18	63297672	A	G	0.335	0.013	0.002	7.4e-14	BMI	Yengo	non-COJO	No
rs8089514	18	69224478	A	T	0.359	0.013	0.002	1.1e-11	BMI	Yengo	non-COJO	Yes
rs11150911	18	73498528	A	C	0.281	0.013	0.002	4.7e-13	BMI	Yengo	non-COJO	No

rs1787267	18	76742544	C	G	0.063	-0.024	0.004	3.4e-11	BMI	Yengo	non-COJO	Yes
rs1608445	18	947954	A	G	0.435	-0.010	0.002	3.7e-09	BMI	Yengo	non-COJO	No
rs12609744	19	12994140	T	C	0.693	-0.013	0.002	3.6e-11	BMI	Yengo	non-COJO	Yes
rs273504	19	18215247	A	G	0.573	-0.015	0.002	4.4e-18	BMI	Yengo	non-COJO	No
rs17724992	19	18454825	A	G	0.740	0.018	0.002	1e-22	BMI	Yengo	non-COJO	No
rs757318	19	18820308	A	C	0.480	-0.018	0.002	2.4e-29	BMI	Yengo	non-COJO	Yes
rs998732	19	19378671	A	G	0.842	0.017	0.002	2e-14	BMI	Yengo	non-COJO	No
rs2304130	19	19789528	A	G	0.915	0.018	0.003	2.9e-09	BMI	Yengo	non-COJO	Yes
rs8102137	19	30296853	T	C	0.676	-0.019	0.002	1.7e-25	BMI	Yengo	non-COJO	No
rs2866816	19	30683879	T	C	0.739	0.013	0.002	5.6e-11	BMI	Yengo	non-COJO	Yes
rs11668301	19	31016196	A	G	0.848	0.021	0.002	1.9e-18	BMI	Yengo	non-COJO	No
rs10408013	19	33963766	T	C	0.291	0.011	0.002	8e-10	BMI	Yengo	non-COJO	Yes
rs29938	19	34311481	T	C	0.328	-0.015	0.002	6.7e-18	BMI	Yengo	non-COJO	Yes
rs895330	19	4060707	C	G	0.808	0.020	0.002	5.5e-19	BMI	Yengo	non-COJO	No
rs3826705	19	42637232	T	C	0.879	-0.016	0.003	6.6e-09	BMI	Yengo	non-COJO	No
rs2075650	19	45395619	A	G	0.861	0.024	0.002	1.5e-25	BMI	Yengo	non-COJO	No

rs11672660	19	46180184	T	C	0.205	-0.034	0.002	1.7e-60	BMI	Yengo	non-COJO	Yes
rs3810291	19	47569003	A	G	0.670	0.027	0.002	2.1e-52	BMI	Yengo	non-COJO	Yes
rs1884389	20	1410582	T	C	0.429	-0.010	0.002	4e-09	BMI	Yengo	non-COJO	No
rs8123881	20	15819495	A	G	0.870	-0.020	0.002	4.4e-16	BMI	Yengo	non-COJO	No
rs4814512	20	16564210	A	C	0.782	0.013	0.002	2.3e-10	BMI	Yengo	non-COJO	Yes
rs6138482	20	25059442	T	C	0.197	0.015	0.002	5.8e-13	BMI	Yengo	non-COJO	No
rs676749	20	3026069	A	T	0.502	-0.010	0.002	1.7e-09	BMI	Yengo	non-COJO	No
rs6121381	20	30785593	A	T	0.847	-0.015	0.002	9.4e-10	BMI	Yengo	non-COJO	Yes
rs13041173	20	32542814	A	G	0.659	-0.011	0.002	5e-09	BMI	Yengo	non-COJO	Yes
rs6142096	20	32686658	A	G	0.528	0.014	0.002	1.8e-15	BMI	Yengo	non-COJO	Yes
rs2425241	20	35018412	T	C	0.067	-0.020	0.003	2.7e-09	BMI	Yengo	non-COJO	Yes
rs2143253	20	41987392	A	G	0.119	-0.019	0.003	1.1e-12	BMI	Yengo	non-COJO	No
rs2425857	20	44914134	A	G	0.441	0.012	0.002	2.8e-11	BMI	Yengo	non-COJO	No
rs6019482	20	47495560	T	C	0.165	-0.018	0.002	2.8e-14	BMI	Yengo	non-COJO	Yes
rs17806379	20	51107290	T	C	0.179	-0.026	0.002	1.5e-30	BMI	Yengo	non-COJO	No
rs1512065	20	53453326	A	G	0.237	0.014	0.002	5.7e-11	BMI	Yengo	non-COJO	Yes
rs559267	20	54157497	A	G	0.664	-0.012	0.002	3e-11	BMI	Yengo	non-COJO	No

rs6011457	20	61530915	A	T	0.498	-0.012	0.002	2.7e-11	BMI	Yengo	non-COJO	Yes
rs310618	20	62127121	T	C	0.671	-0.011	0.002	5.5e-09	BMI	Yengo	non-COJO	No
rs1884897	20	6612832	A	G	0.369	-0.019	0.002	1.3e-30	BMI	Yengo	non-COJO	No
rs762147	21	39238610	A	G	0.271	-0.012	0.002	3.3e-09	BMI	Yengo	non-COJO	No
rs13047416	21	40309436	C	G	0.623	0.015	0.002	2.2e-17	BMI	Yengo	non-COJO	Yes
rs2836961	21	40627020	A	C	0.616	-0.010	0.002	1.1e-09	BMI	Yengo	non-COJO	No
rs2838006	21	42653567	T	C	0.362	-0.013	0.002	5.4e-12	BMI	Yengo	non-COJO	No
rs427943	21	46570896	A	C	0.433	-0.017	0.002	7.3e-23	BMI	Yengo	non-COJO	Yes
rs4820408	22	40604945	T	G	0.408	0.015	0.002	2.1e-19	BMI	Yengo	non-COJO	No
rs9615905	22	48875699	T	C	0.450	0.011	0.002	2.7e-10	BMI	Yengo	non-COJO	No
rs2061708	1	103417203	G	C	0.588	0.015	0.002	2.127e-14	WHR	Pulit		Yes
rs2335077	1	107573565	A	G	0.645	-0.012	0.002	8.334e-11	WHR	Pulit		No
rs6658723	1	112274162	T	C	0.433	0.014	0.002	2.343e-13	WHR	Pulit		No
rs6694768	1	114953420	T	C	0.682	0.012	0.002	1.621e-10	WHR	Pulit		Yes
rs10923724	1	119546842	C	T	0.556	0.024	0.002	1.81e-45	WHR	Pulit		No
rs905938	1	154991389	T	C	0.724	0.013	0.002	7.831e-11	WHR	Pulit		No
rs6688053	1	163589208	C	T	0.444	0.012	0.002	4.434e-10	WHR	Pulit		No

rs10919388	1	170372503	A	C	0.273	-0.027	0.002	6.402e-43	WHR	Pulit	Yes
rs12138803	1	172348823	C	T	0.200	0.020	0.002	7.185e-25	WHR	Pulit	No
rs543874	1	177889480	A	G	0.780	-0.020	0.002	8.143e-22	WHR	Pulit	No
rs12024554	1	19925759	C	T	0.235	-0.015	0.002	1.077e-10	WHR	Pulit	No
rs6658424	1	200049302	T	A	0.284	-0.012	0.002	1.357e-10	WHR	Pulit	No
rs3903399	1	205041542	T	C	0.785	-0.015	0.002	6.817e-12	WHR	Pulit	Yes
rs3767848	1	214173840	G	A	0.254	-0.012	0.002	2.161e-09	WHR	Pulit	No
rs1563355	1	219653101	T	C	0.328	-0.028	0.002	1.591e-49	WHR	Pulit	Yes
rs6604731	1	224051439	C	T	0.300	-0.012	0.002	2.546e-09	WHR	Pulit	Yes
rs2903995	1	23271504	T	A	0.378	-0.012	0.002	1.607e-11	WHR	Pulit	No
rs12042959	1	243533273	A	G	0.863	0.016	0.002	9.25e-10	WHR	Pulit	No
rs213624	1	26201164	G	A	0.526	0.012	0.002	3.294e-11	WHR	Pulit	No
rs2742690	1	2987268	C	A	0.200	0.017	0.002	9.216e-12	WHR	Pulit	No
rs4660808	1	40018509	C	T	0.223	0.014	0.002	7.577e-12	WHR	Pulit	No
rs946106	1	49928489	C	T	0.766	-0.017	0.002	2.719e-17	WHR	Pulit	Yes
rs12140153	1	62579891	G	T	0.091	-0.021	0.004	7.637e-10	WHR	Pulit	No

rs2613505	1	72835410	C	T	0.820	0.016	0.002	1.012e-13	WHR	Pulit	No
rs313741	1	86273451	A	T	0.551	-0.012	0.002	1.626e-11	WHR	Pulit	No
rs6699397	1	91212216	A	G	0.624	-0.012	0.002	1.276e-11	WHR	Pulit	Yes
rs6688233	1	9335745	C	T	0.239	0.019	0.002	3.021e-19	WHR	Pulit	Yes
rs9659380	1	98423149	G	A	0.837	-0.018	0.002	5.222e-14	WHR	Pulit	No
rs4851284	2	100894887	C	T	0.668	-0.015	0.002	5.616e-13	WHR	Pulit	No
rs1345203	2	112253851	T	C	0.783	0.019	0.002	3.068e-15	WHR	Pulit	No
rs4372913	2	114517748	A	G	0.788	-0.014	0.002	8.599e-11	WHR	Pulit	No
rs332105	2	119444229	G	A	0.554	-0.014	0.002	1.119e-14	WHR	Pulit	No
rs711869	2	13073967	G	A	0.557	-0.017	0.002	2.375e-21	WHR	Pulit	No
rs55920843	2	158412701	T	G	0.989	0.062	0.009	1.549e-11	WHR	Pulit	No
rs1020731	2	161144055	G	A	0.702	0.013	0.002	5.838e-11	WHR	Pulit	No
rs12621633	2	162859436	G	A	0.011	0.054	0.009	2.996e-09	WHR	Pulit	Yes
rs399984	2	164877930	C	G	0.779	0.013	0.002	1.862e-09	WHR	Pulit	Yes
rs409125	2	165667643	T	A	0.628	-0.018	0.002	2.083e-23	WHR	Pulit	Yes
rs12469667	2	166162705	G	A	0.232	-0.013	0.002	2.821e-10	WHR	Pulit	No
rs9630986	2	181607751	G	C	0.668	0.012	0.002	1.017e-10	WHR	Pulit	No

rs1569135	2	188115398	A	G	0.537	0.022	0.002	2.758e-37	WHR	Pulit	Yes
rs1124639	2	200775744	T	C	0.439	-0.011	0.002	7.475e-11	WHR	Pulit	No
rs7599312	2	213413231	G	A	0.273	-0.011	0.002	2.358e-09	WHR	Pulit	No
rs1017698	2	219170525	G	A	0.597	-0.011	0.002	5.13e-10	WHR	Pulit	No
rs17324331	2	230739209	G	C	0.314	0.012	0.002	1.79e-10	WHR	Pulit	No
rs3891424	2	239365456	G	A	0.053	-0.028	0.004	3.997e-10	WHR	Pulit	No
rs6749646	2	25193998	A	T	0.780	-0.021	0.002	5.985e-22	WHR	Pulit	No
rs10153926	2	43189120	G	A	0.219	0.014	0.002	2.003e-09	WHR	Pulit	No
rs7591387	2	43756032	C	T	0.102	0.018	0.003	9.298e-11	WHR	Pulit	Yes
rs17326656	2	48962291	G	T	0.235	0.015	0.002	4.166e-13	WHR	Pulit	No
rs929641	2	58792377	A	G	0.589	0.013	0.002	7.979e-14	WHR	Pulit	No
rs6545714	2	59307725	G	A	0.611	-0.014	0.002	8.963e-16	WHR	Pulit	No
rs13028903	2	59951465	C	T	0.460	0.011	0.002	2.752e-10	WHR	Pulit	Yes
rs2419407	2	60170875	C	T	0.565	0.010	0.002	3.854e-09	WHR	Pulit	Yes
rs2195086	2	60814466	T	G	0.833	-0.014	0.002	2.809e-09	WHR	Pulit	Yes
rs6743060	2	629510	C	A	0.842	0.027	0.002	1.795e-32	WHR	Pulit	No
rs1385167	2	66200648	A	G	0.862	-0.022	0.002	6.224e-20	WHR	Pulit	Yes

rs11897119	2	66772000	T	C	0.594	-0.013	0.002	4.068e-15	WHR	Pulit	No
rs4671193	2	67846288	C	T	0.356	-0.019	0.002	4.792e-25	WHR	Pulit	Yes
rs12692387	2	9698190	T	C	0.332	-0.012	0.002	2.896e-09	WHR	Pulit	No
rs2595004	3	11406721	C	T	0.825	-0.016	0.002	2.062e-11	WHR	Pulit	Yes
rs9878908	3	12302462	C	T	0.813	-0.019	0.002	3.382e-20	WHR	Pulit	Yes
rs6795831	3	129341403	A	C	0.814	0.029	0.002	2.091e-37	WHR	Pulit	No
rs13063979	3	131564741	T	G	0.732	-0.014	0.002	1.194e-12	WHR	Pulit	No
rs645040	3	135926622	G	T	0.770	0.016	0.002	1.154e-14	WHR	Pulit	No
rs9844972	3	150097635	G	C	0.065	0.028	0.004	1.118e-14	WHR	Pulit	No
rs10049088	3	156797648	C	T	0.381	-0.027	0.002	1.472e-53	WHR	Pulit	Yes
rs2455848	3	15771372	T	C	0.314	0.013	0.002	1.827e-12	WHR	Pulit	Yes
rs12494190	3	168949384	G	A	0.404	-0.012	0.002	3.034e-11	WHR	Pulit	No
rs4894803	3	171800256	A	G	0.600	0.015	0.002	3.743e-16	WHR	Pulit	No
rs7647305	3	185834290	T	C	0.210	-0.014	0.002	8.28e-12	WHR	Pulit	No
rs6550597	3	18738940	G	A	0.719	0.012	0.002	3.083e-09	WHR	Pulit	No
rs12629247	3	187632584	G	C	0.040	0.029	0.005	9.83e-10	WHR	Pulit	Yes

rs12631066	3	33872787	G	C	0.225	0.012	0.002	2.089e-09	WHR	Pulit	No
rs10490869	3	35635145	A	T	0.796	-0.018	0.002	9.338e-17	WHR	Pulit	Yes
rs155524	3	37562141	G	A	0.590	0.013	0.002	1.275e-13	WHR	Pulit	Yes
rs2291542	3	49751585	C	T	0.327	0.017	0.002	1.74e-20	WHR	Pulit	No
rs1452075	3	62481063	C	T	0.732	0.012	0.002	1.319e-10	WHR	Pulit	No
rs76699125	3	64701535	T	C	0.937	0.032	0.004	4.955e-15	WHR	Pulit	No
rs6548834	3	82704753	G	A	0.363	0.012	0.002	1.642e-10	WHR	Pulit	No
rs12495178	3	85886077	T	C	0.642	0.012	0.002	1.321e-12	WHR	Pulit	Yes
rs9942009	3	89121921	C	T	0.380	0.013	0.002	3.033e-12	WHR	Pulit	No
rs4686340	3	9345218	A	C	0.251	0.012	0.002	6.014e-10	WHR	Pulit	No
rs793456	3	99525631	G	A	0.604	-0.011	0.002	3.563e-09	WHR	Pulit	No
rs1789882	4	100235053	A	G	0.169	0.016	0.002	9.974e-12	WHR	Pulit	No
rs809955	4	140874760	G	A	0.367	-0.016	0.002	2.482e-14	WHR	Pulit	No
rs789351	4	145868370	C	T	0.420	0.012	0.002	7.567e-13	WHR	Pulit	No
rs10019888	4	26062990	A	G	0.813	-0.021	0.002	8.047e-20	WHR	Pulit	No
rs17644283	4	26308792	A	G	0.388	0.015	0.002	3.237e-17	WHR	Pulit	No
rs3121419	4	3232257	C	T	0.297	-0.013	0.002	1.59e-11	WHR	Pulit	Yes

rs13130484	4	45175691	C	T	0.429	0.015	0.002	7.834e-18	WHR	Pulit	No
rs861029	4	56245637	T	C	0.749	-0.014	0.002	4.364e-11	WHR	Pulit	No
rs2167750	4	89730074	C	T	0.473	0.020	0.002	6.473e-29	WHR	Pulit	No
rs11724804	4	965779	G	A	0.444	-0.016	0.002	4.979e-20	WHR	Pulit	No
rs2161097	5	103945178	C	T	0.441	0.013	0.002	2.107e-12	WHR	Pulit	No
rs4395620	5	106328326	T	C	0.576	0.011	0.002	3.568e-09	WHR	Pulit	No
rs1822489	5	112542527	A	G	0.318	0.012	0.002	1.521e-10	WHR	Pulit	No
rs1045241	5	118729286	C	T	0.282	-0.012	0.002	8.856e-11	WHR	Pulit	No
rs11747001	5	132412299	A	G	0.764	0.015	0.002	8.389e-15	WHR	Pulit	No
rs4454042	5	155824774	T	C	0.273	0.013	0.002	1.368e-10	WHR	Pulit	No
rs1122080	5	158015903	G	A	0.204	-0.013	0.002	1.603e-09	WHR	Pulit	No
rs17738166	5	172997978	G	A	0.397	0.011	0.002	3.779e-10	WHR	Pulit	No
rs10070064	5	173281777	C	T	0.264	0.018	0.002	3.814e-18	WHR	Pulit	Yes
rs244723	5	176534886	G	A	0.529	0.015	0.002	8.915e-14	WHR	Pulit	Yes
rs10475249	5	4010135	C	G	0.549	0.013	0.002	1.292e-11	WHR	Pulit	No
rs2448	5	53302354	T	C	0.738	0.016	0.002	4.621e-15	WHR	Pulit	No
rs3936510	5	55860866	G	T	0.197	0.024	0.002	1.756e-29	WHR	Pulit	Yes

rs34699	5	66304225	G	T	0.581	-0.012	0.002	4.415e-11	WHR	Pulit	Yes
rs2112347	5	75015242	T	G	0.630	0.015	0.002	8.407e-18	WHR	Pulit	No
rs1382894	5	76599022	A	T	0.649	0.011	0.002	9.152e-10	WHR	Pulit	Yes
rs2161228	5	88001798	C	T	0.102	0.019	0.003	4.317e-11	WHR	Pulit	No
rs2503099	6	100610101	A	G	0.835	-0.021	0.002	8.298e-20	WHR	Pulit	No
rs12206094	6	108906200	C	T	0.289	-0.012	0.002	2.207e-10	WHR	Pulit	No
rs2357760	6	120213880	G	A	0.674	0.011	0.002	3.804e-10	WHR	Pulit	No
rs72959041	6	127454893	G	A	0.041	0.126	0.004	4.56e-183	WHR	Pulit	Yes
rs605066	6	139829666	C	T	0.583	-0.019	0.002	2.381e-26	WHR	Pulit	No
rs9296938	6	14573063	A	G	0.250	-0.014	0.002	1.502e-12	WHR	Pulit	No
rs112266013	6	15230743	G	A	0.141	-0.017	0.003	3.168e-09	WHR	Pulit	No
rs672341	6	153455994	G	A	0.413	-0.012	0.002	7.964e-10	WHR	Pulit	No
rs668871	6	160769811	C	T	0.469	-0.013	0.002	7.192e-12	WHR	Pulit	Yes
rs7744833	6	20581828	A	G	0.682	0.012	0.002	6.875e-11	WHR	Pulit	Yes
rs2894204	6	31237061	C	T	0.638	0.021	0.002	8.006e-25	WHR	Pulit	No
rs114760566	6	34192036	C	A	0.043	0.067	0.005	2.944e-44	WHR	Pulit	Yes

rs2033529	6	40348653	A	G	0.725	-0.015	0.002	2.375e-16	WHR	Pulit	Yes
rs4714668	6	43101270	C	G	0.530	-0.012	0.002	2.529e-09	WHR	Pulit	No
rs6905288	6	43758873	G	A	0.574	0.033	0.002	2.015e-78	WHR	Pulit	Yes
rs9369425	6	43810974	G	A	0.708	0.020	0.002	1.089e-23	WHR	Pulit	Yes
rs987237	6	50803050	A	G	0.844	-0.020	0.002	9.975e-20	WHR	Pulit	Yes
rs9370243	6	53789830	G	T	0.080	0.020	0.003	1.131e-09	WHR	Pulit	No
rs1294436	6	6746166	G	C	0.597	0.023	0.002	1.287e-30	WHR	Pulit	No
rs1334576	6	7211818	G	A	0.425	-0.016	0.002	1.66e-19	WHR	Pulit	Yes
rs12527712	6	80916967	C	T	0.088	0.028	0.003	3.377e-18	WHR	Pulit	No
rs9362083	6	85396119	T	A	0.587	-0.012	0.002	7.838e-11	WHR	Pulit	Yes
rs17448885	6	97385975	C	G	0.652	0.011	0.002	3.325e-09	WHR	Pulit	No
rs10499013	6	97946396	G	A	0.280	-0.012	0.002	5.096e-10	WHR	Pulit	No
rs901630	6	98539519	C	T	0.411	-0.012	0.002	6.814e-12	WHR	Pulit	Yes
rs372321	7	101721006	G	A	0.178	0.016	0.002	1.72e-11	WHR	Pulit	No
rs1142	7	104756326	C	T	0.334	0.015	0.002	2.057e-17	WHR	Pulit	Yes
rs4727695	7	107614003	A	G	0.899	0.022	0.003	1.846e-13	WHR	Pulit	Yes
rs4476935	7	112987650	C	T	0.427	-0.011	0.002	1.54e-09	WHR	Pulit	No

rs39312	7	116954785	A	C	0.620	-0.015	0.002	3.496e-18	WHR	Pulit	No
rs6942652	7	120889272	G	C	0.429	-0.013	0.002	2.182e-12	WHR	Pulit	No
rs13229637	7	136717447	T	C	0.854	0.016	0.002	1.907e-10	WHR	Pulit	No
rs1534696	7	26397239	C	A	0.569	-0.023	0.002	3.674e-39	WHR	Pulit	No
rs2715135	7	50750128	T	G	0.371	0.011	0.002	4.092e-09	WHR	Pulit	No
rs7797307	7	68686127	G	C	0.060	-0.024	0.004	7.072e-10	WHR	Pulit	No
rs55747707	7	73037366	G	A	0.176	-0.015	0.002	3.396e-11	WHR	Pulit	No
rs11764879	7	77333267	G	A	0.286	-0.012	0.002	3.926e-10	WHR	Pulit	Yes
rs13256367	8	128334900	A	C	0.653	0.014	0.002	5.415e-14	WHR	Pulit	No
rs15285	8	19824667	C	T	0.263	-0.012	0.002	1.619e-09	WHR	Pulit	No
rs9644033	8	23610639	A	T	0.754	0.019	0.002	2.101e-19	WHR	Pulit	No
rs11992444	8	25464690	G	T	0.508	0.018	0.002	4.99e-21	WHR	Pulit	No
rs7823561	8	25641764	A	C	0.653	0.016	0.002	3.258e-17	WHR	Pulit	Yes
rs2725371	8	30854033	A	G	0.300	0.017	0.002	9.9e-16	WHR	Pulit	Yes
rs36061954	8	38329650	C	T	0.398	0.015	0.002	3.421e-13	WHR	Pulit	No
rs62506196	8	60264465	A	C	0.838	-0.016	0.003	2.696e-09	WHR	Pulit	No
rs13255070	8	68203608	A	G	0.719	-0.014	0.002	5.072e-10	WHR	Pulit	No

rs28446899	8	72396213	C	T	0.078	0.036	0.004	7.917e-23	WHR	Pulit	No
rs1431659	8	73439070	A	G	0.274	0.014	0.002	1.121e-12	WHR	Pulit	Yes
rs62565259	9	102162570	C	T	0.165	-0.016	0.003	3.706e-09	WHR	Pulit	Yes
rs1800978	9	107665978	C	G	0.879	0.020	0.003	9.181e-15	WHR	Pulit	No
rs10991433	9	107726918	T	C	0.896	-0.025	0.003	5.731e-20	WHR	Pulit	Yes
rs12684047	9	111972671	T	A	0.191	-0.018	0.002	3.439e-15	WHR	Pulit	No
rs10980797	9	113912553	A	G	0.519	-0.015	0.002	3.881e-15	WHR	Pulit	No
rs7025089	9	134881443	C	A	0.679	-0.012	0.002	4.288e-10	WHR	Pulit	No
rs6474945	9	15670492	G	T	0.454	-0.010	0.002	2.669e-09	WHR	Pulit	No
rs2183825	9	28412375	T	C	0.686	-0.014	0.002	4.425e-15	WHR	Pulit	No
rs1974004	9	95568230	C	T	0.153	0.017	0.002	3.846e-12	WHR	Pulit	No
rs2398893	9	96758342	A	G	0.714	0.016	0.002	9.007e-17	WHR	Pulit	No
rs12777288	10	115860058	T	C	0.771	-0.014	0.002	6.882e-11	WHR	Pulit	No
rs17101456	10	122875040	A	G	0.879	-0.021	0.003	7.456e-14	WHR	Pulit	No
rs1243188	10	21908803	T	C	0.706	-0.015	0.002	2.371e-14	WHR	Pulit	No
rs1494204	10	27904321	C	T	0.419	-0.011	0.002	4.406e-09	WHR	Pulit	No

rs10827252	10	33672884	A	G	0.493	-0.011	0.002	2.031e-10	WHR	Pulit	No
rs1757471	10	34168090	C	T	0.508	0.013	0.002	5.891e-13	WHR	Pulit	Yes
rs708437	10	36227656	G	A	0.826	0.014	0.002	1.598e-09	WHR	Pulit	No
rs12774134	10	4963327	C	T	0.119	-0.016	0.003	2.096e-09	WHR	Pulit	No
rs7907173	10	5648787	G	A	0.451	-0.011	0.002	9.433e-10	WHR	Pulit	Yes
rs7070670	10	61842645	C	T	0.323	-0.013	0.002	3.644e-10	WHR	Pulit	No
rs7070749	10	63882682	G	A	0.553	0.013	0.002	1.88e-10	WHR	Pulit	Yes
rs10761785	10	65318766	G	T	0.514	-0.015	0.002	6.427e-18	WHR	Pulit	No
rs780159	10	80907147	A	G	0.429	-0.013	0.002	2.861e-14	WHR	Pulit	No
rs10788569	10	89604732	T	C	0.724	-0.013	0.002	3.975e-12	WHR	Pulit	No
rs950732	10	94114633	C	T	0.575	0.012	0.002	2.376e-11	WHR	Pulit	Yes
rs11187537	10	95346805	G	C	0.263	0.013	0.002	1.729e-10	WHR	Pulit	No
rs10840349	11	10076430	A	G	0.507	-0.012	0.002	4.93e-10	WHR	Pulit	Yes
rs2513987	11	102977271	G	A	0.269	-0.014	0.002	3.882e-10	WHR	Pulit	No
rs2957658	11	10393468	G	A	0.491	-0.012	0.002	1.841e-10	WHR	Pulit	No
rs2276390	11	111895254	G	T	0.338	-0.021	0.002	5.76e-28	WHR	Pulit	Yes
rs719802	11	113234679	T	C	0.397	0.011	0.002	3.793e-10	WHR	Pulit	No

rs11216183	11	116781545	C	A	0.092	0.023	0.003	2.711e-11	WHR	Pulit	No
rs3825061	11	118944675	C	T	0.387	0.014	0.002	5.454e-15	WHR	Pulit	Yes
rs579682	11	122014110	C	T	0.714	-0.013	0.002	2.022e-11	WHR	Pulit	Yes
rs747249	11	130271647	A	G	0.359	0.011	0.002	2.65e-09	WHR	Pulit	No
rs747601	11	13274553	A	T	0.275	-0.013	0.002	7.274e-11	WHR	Pulit	Yes
rs11030108	11	27695464	A	G	0.331	0.015	0.002	1.214e-17	WHR	Pulit	No
rs13642	11	30432220	A	T	0.645	0.011	0.002	9.486e-10	WHR	Pulit	No
rs4755720	11	43628749	C	T	0.611	-0.013	0.002	3.975e-13	WHR	Pulit	No
rs12287076	11	47606865	G	C	0.625	0.019	0.002	3.529e-21	WHR	Pulit	Yes
rs11231084	11	62177643	C	G	0.494	-0.012	0.002	2.409e-09	WHR	Pulit	No
rs2509967	11	62312786	C	G	0.634	-0.015	0.002	1.022e-16	WHR	Pulit	No
rs35169799	11	64031241	C	T	0.062	0.037	0.004	6.257e-20	WHR	Pulit	Yes
rs10896012	11	65278461	T	C	0.785	-0.018	0.002	2.147e-16	WHR	Pulit	Yes
rs7395513	11	69262756	G	A	0.439	-0.017	0.002	2.458e-18	WHR	Pulit	Yes
rs140201358	11	823586	C	G	0.987	-0.056	0.009	8.253e-11	WHR	Pulit	No
rs536665	11	85322400	A	G	0.798	-0.017	0.002	2.183e-12	WHR	Pulit	No
rs12575252	11	8694073	G	C	0.334	-0.015	0.002	2.316e-18	WHR	Pulit	Yes

rs10507223	12	108455828	C	G	0.767	0.013	0.002	5.095e-10	WHR	Pulit	Yes
rs4964656	12	108594069	G	C	0.303	-0.018	0.002	1.957e-20	WHR	Pulit	No
rs863750	12	124505444	C	T	0.584	0.026	0.002	6.195e-51	WHR	Pulit	No
rs34322	12	12879570	T	C	0.466	0.010	0.002	4.604e-09	WHR	Pulit	No
rs11055887	12	14417179	G	A	0.193	-0.013	0.002	4.281e-09	WHR	Pulit	Yes
rs7222	12	2055266	T	C	0.499	0.011	0.002	1.169e-09	WHR	Pulit	No
rs10842707	12	26471364	C	T	0.204	0.027	0.002	3.911e-39	WHR	Pulit	No
rs10843817	12	30865510	A	C	0.760	0.013	0.002	5.847e-10	WHR	Pulit	Yes
rs2200155	12	33734935	G	A	0.372	-0.013	0.002	5.074e-13	WHR	Pulit	No
rs1458156	12	41887940	C	T	0.496	0.012	0.002	1.856e-12	WHR	Pulit	Yes
rs7138803	12	50247468	G	A	0.384	0.012	0.002	1.089e-12	WHR	Pulit	No
rs10876528	12	54421476	C	A	0.351	0.024	0.002	8.584e-39	WHR	Pulit	No
rs11176015	12	66441684	C	T	0.293	0.015	0.002	7.208e-14	WHR	Pulit	No
rs704061	12	89771903	T	C	0.552	-0.012	0.002	4.367e-11	WHR	Pulit	No
rs1805740	12	9075014	G	T	0.718	-0.014	0.002	5.636e-12	WHR	Pulit	Yes
rs10745659	12	94092690	C	G	0.561	-0.013	0.002	1.427e-12	WHR	Pulit	Yes

rs7311622	12	98772975	C	T	0.453	-0.012	0.002	2.959e-11	WHR	Pulit	No
rs12828016	12	998365	G	T	0.391	-0.011	0.002	4.081e-10	WHR	Pulit	No
rs664532	13	110932363	T	C	0.379	0.011	0.002	1.667e-09	WHR	Pulit	No
rs9515201	13	111040798	A	C	0.307	-0.012	0.002	6.633e-11	WHR	Pulit	Yes
rs1163627	13	112225701	C	A	0.545	0.010	0.002	3.008e-09	WHR	Pulit	Yes
rs1045411	13	31033232	C	T	0.279	-0.016	0.002	1.266e-15	WHR	Pulit	No
rs797486	13	51221618	C	A	0.894	0.032	0.003	1.089e-34	WHR	Pulit	No
rs564930	13	54756074	T	C	0.123	0.020	0.003	1.572e-11	WHR	Pulit	Yes
rs12430764	13	93896935	G	A	0.516	0.011	0.002	1.872e-09	WHR	Pulit	No
rs12590238	14	103350197	C	G	0.834	-0.014	0.002	1.546e-09	WHR	Pulit	No
rs10132280	14	25928179	C	A	0.311	-0.012	0.002	3.114e-10	WHR	Pulit	No
rs1190982	14	58815839	T	C	0.303	0.016	0.002	5.104e-16	WHR	Pulit	No
rs2898885	14	65421274	T	C	0.809	-0.014	0.002	8.513e-10	WHR	Pulit	Yes
rs2526886	14	71359064	G	T	0.690	0.012	0.002	3.646e-09	WHR	Pulit	No
rs17109256	14	79939993	G	A	0.232	0.017	0.002	2.403e-16	WHR	Pulit	No
rs7492628	14	91547136	C	G	0.680	-0.012	0.002	7.893e-11	WHR	Pulit	No
rs4779526	15	31705683	A	T	0.757	0.013	0.002	2.086e-10	WHR	Pulit	No

rs2928140	15	40990353	G	C	0.455	0.012	0.002	2.46e-10	WHR	Pulit	Yes
rs12440605	15	42102285	G	A	0.524	0.012	0.002	4.022e-11	WHR	Pulit	No
rs3736485	15	51748610	A	G	0.456	0.012	0.002	3.846e-12	WHR	Pulit	No
rs10851523	15	53044002	G	C	0.274	-0.012	0.002	1.787e-09	WHR	Pulit	No
rs16976932	15	56781255	G	A	0.120	0.019	0.003	1.026e-11	WHR	Pulit	Yes
rs12440695	15	62435156	T	C	0.615	-0.010	0.002	4.353e-09	WHR	Pulit	No
rs1440372	15	67033151	T	C	0.267	-0.014	0.002	5.081e-13	WHR	Pulit	No
rs8043060	15	67661784	G	A	0.222	-0.017	0.002	8.931e-17	WHR	Pulit	Yes
rs2660824	15	73618309	C	T	0.461	-0.011	0.002	2.715e-10	WHR	Pulit	No
rs7183908	15	74329193	T	C	0.507	-0.016	0.002	8.25e-16	WHR	Pulit	Yes
rs936226	15	75069282	C	T	0.729	0.011	0.002	1.95e-09	WHR	Pulit	Yes
rs12593088	15	81058640	G	A	0.311	-0.013	0.002	5.159e-12	WHR	Pulit	Yes
rs12101393	15	92570921	C	G	0.786	0.014	0.002	1.187e-10	WHR	Pulit	No
rs8024294	15	94023132	G	A	0.112	0.018	0.003	3.624e-10	WHR	Pulit	Yes
rs13333747	16	2175373	T	C	0.817	0.018	0.002	1.418e-12	WHR	Pulit	No
rs7186893	16	24806420	G	T	0.264	-0.014	0.002	1.21e-11	WHR	Pulit	No
rs7498665	16	28883241	A	G	0.618	-0.017	0.002	1.13e-22	WHR	Pulit	Yes

rs4788204	16	29995218	G	A	0.459	0.017	0.002	2.638e-21	WHR	Pulit	No
rs1139653	16	4484396	A	T	0.285	0.015	0.002	1.145e-13	WHR	Pulit	Yes
rs8060576	16	4908956	C	T	0.123	0.016	0.003	1.496e-09	WHR	Pulit	No
rs2047937	16	49864791	C	T	0.517	-0.011	0.002	4.573e-10	WHR	Pulit	No
rs9923544	16	53801985	C	T	0.435	0.039	0.002	1.18e-113	WHR	Pulit	Yes
rs9302652	16	53865975	C	T	0.734	-0.015	0.002	3.813e-15	WHR	Pulit	No
rs889398	16	69556715	C	T	0.415	-0.017	0.002	1.985e-23	WHR	Pulit	No
rs2925979	16	81534790	T	C	0.296	0.022	0.002	1.623e-31	WHR	Pulit	No
rs7206608	16	82872628	C	G	0.675	-0.013	0.002	2.481e-11	WHR	Pulit	No
rs7198287	16	85258191	C	T	0.218	-0.014	0.002	6.096e-10	WHR	Pulit	Yes
rs4646342	17	17493272	G	A	0.454	-0.013	0.002	6.61e-13	WHR	Pulit	No
rs7213608	17	21279289	C	T	0.683	-0.017	0.002	6.951e-19	WHR	Pulit	Yes
rs7217226	17	2136065	T	G	0.656	-0.014	0.002	9.937e-15	WHR	Pulit	No
rs2306589	17	34848874	T	C	0.473	0.016	0.002	2.521e-21	WHR	Pulit	No
rs8070737	17	3981066	G	T	0.168	0.016	0.002	7.386e-12	WHR	Pulit	No
rs591939	17	40698075	A	G	0.755	-0.018	0.002	9.11e-15	WHR	Pulit	No

rs17651507	17	44059010	A	T	0.727	0.019	0.002	1.855e-20	WHR	Pulit	Yes
rs8071778	17	46080233	G	C	0.154	-0.016	0.002	6.622e-11	WHR	Pulit	No
rs758598	17	59492714	A	G	0.330	0.012	0.002	5.587e-11	WHR	Pulit	No
rs8075273	17	61728881	C	A	0.287	-0.014	0.002	2.757e-13	WHR	Pulit	Yes
rs12449442	17	65947640	G	A	0.219	0.017	0.002	2.554e-16	WHR	Pulit	Yes
rs11654387	17	68446861	C	G	0.488	0.016	0.002	1.453e-19	WHR	Pulit	Yes
rs9988	17	73230856	C	T	0.835	0.015	0.002	1.934e-10	WHR	Pulit	No
rs8079062	17	74255029	A	G	0.921	-0.023	0.003	1.668e-12	WHR	Pulit	No
rs858516	17	7537098	C	T	0.547	-0.012	0.002	1.628e-09	WHR	Pulit	Yes
rs4239275	17	79923718	T	C	0.413	0.012	0.002	3.261e-11	WHR	Pulit	Yes
rs1787013	18	13072979	T	C	0.559	-0.011	0.002	1.327e-09	WHR	Pulit	No
rs62095889	18	21069068	G	A	0.343	-0.017	0.002	1.623e-15	WHR	Pulit	Yes
rs10164099	18	34690744	T	C	0.874	-0.015	0.002	1.173e-09	WHR	Pulit	No
rs1158805	18	40736590	C	A	0.380	-0.013	0.002	4.947e-13	WHR	Pulit	No
rs494752	18	46853270	G	C	0.655	-0.015	0.002	2.313e-16	WHR	Pulit	No
rs6566233	18	53445930	T	C	0.515	-0.013	0.002	7.126e-11	WHR	Pulit	No
rs6567160	18	57829135	T	C	0.753	-0.026	0.002	2.53e-39	WHR	Pulit	No

rs12608504	19	18389135	A	G	0.359	0.025	0.002	4.675e-46	WHR	Pulit	No
rs12986231	19	18469017	T	C	0.729	0.015	0.002	2.044e-11	WHR	Pulit	No
rs11878507	19	18837823	G	A	0.506	-0.012	0.002	1.385e-09	WHR	Pulit	Yes
rs998732	19	19378671	A	G	0.834	0.016	0.002	1.042e-12	WHR	Pulit	No
rs12459350	19	2176586	A	G	0.542	0.013	0.002	2.233e-15	WHR	Pulit	No
rs17513613	19	30286822	T	C	0.691	-0.012	0.002	5.424e-12	WHR	Pulit	No
rs3786897	19	33893008	A	G	0.580	-0.024	0.002	1.451e-43	WHR	Pulit	Yes
rs429358	19	45411941	T	C	0.846	0.035	0.003	4.214e-37	WHR	Pulit	No
rs1800437	19	46181392	G	C	0.188	-0.021	0.002	6.225e-22	WHR	Pulit	No
rs8103017	19	55999142	C	G	0.704	-0.016	0.002	2.244e-14	WHR	Pulit	Yes
rs1035940	19	7199978	C	G	0.276	0.012	0.002	1.468e-09	WHR	Pulit	Yes
rs1406948	20	33905619	G	A	0.368	-0.014	0.002	4.124e-15	WHR	Pulit	No
rs1997833	20	39690342	T	C	0.707	-0.012	0.002	4.219e-11	WHR	Pulit	No
rs6130360	20	42010996	A	G	0.848	0.015	0.002	1.133e-09	WHR	Pulit	No
rs2236519	20	45529571	G	A	0.369	0.021	0.002	1.894e-30	WHR	Pulit	No
rs3092781	20	45789953	C	T	0.451	-0.014	0.002	1.915e-17	WHR	Pulit	Yes
rs6021889	20	50982870	A	G	0.710	0.020	0.002	2.463e-27	WHR	Pulit	No

rs910382	20	51699189	G	A	0.494	-0.017	0.002	2.395e-21	WHR	Pulit	Yes
rs1328757	20	56135199	C	T	0.474	0.011	0.002	1.693e-10	WHR	Pulit	No
rs805768	20	5666891	C	T	0.239	0.014	0.002	3.625e-09	WHR	Pulit	Yes
rs979012	20	6623374	T	C	0.364	0.012	0.002	7.855e-11	WHR	Pulit	No
rs28451064	21	35593827	G	A	0.127	0.018	0.003	4.228e-09	WHR	Pulit	No
rs9976841	21	39484323	G	A	0.387	-0.013	0.002	2.095e-12	WHR	Pulit	No
rs2294239	22	29449477	A	G	0.568	0.020	0.002	3.173e-31	WHR	Pulit	No
rs733381	22	40669648	A	G	0.772	0.012	0.002	2.817e-09	WHR	Pulit	No
rs8141715	22	47214749	T	G	0.754	-0.014	0.002	1.454e-11	WHR	Pulit	No
rs1106529	1	119,333,020	A	G	0.753	0.028	0.004	2.94e-12	WHR	Shungin	No
rs2645294	1	119,376,110	T	C	0.579	0.023	0.003	3.41e-12	WHR	Shungin	Yes
rs714515	1	170,619,613	G	A	0.428	0.019	0.003	1.23e-08	WHR	Shungin	No
rs2820443	1	217,820,132	T	C	0.718	0.026	0.004	3.78e-12	WHR	Shungin	No
rs10195252	2	165,221,337	T	C	0.592	0.020	0.003	2.57e-09	WHR	Shungin	No
rs1128249	2	165,236,870	G	T	0.597	0.021	0.003	1.59e-09	WHR	Shungin	Yes
rs1569135	2	187,823,643	A	G	0.529	0.024	0.003	1e-12	WHR	Shungin	No

rs17451107	3	158,280,303	T	C	0.613	0.023	0.004	3.5e-11	WHR	Shungin	No
rs2371767	3	64,693,298	G	C	0.724	0.023	0.004	3.88e-09	WHR	Shungin	No
rs459193	5	55,842,508	A	G	0.264	0.026	0.004	6.02e-12	WHR	Shungin	No
rs1936805	6	127,493,809	T	C	0.511	0.038	0.003	8.47e-30	WHR	Shungin	No
rs72959041	6	127,496,586	A	G	0.058	0.104	0.012	5.97e-17	WHR	Shungin	Yes
rs998584	6	43,865,874	A	C	0.485	0.029	0.004	4.98e-15	WHR	Shungin	No
rs1358980	6	43,872,529	T	C	0.471	0.027	0.004	1.98e-14	WHR	Shungin	Yes
rs1294410	6	6,683,751	C	T	0.633	0.025	0.003	3.18e-13	WHR	Shungin	No
rs10245353	7	25,825,139	A	C	0.200	0.027	0.004	1.57e-10	WHR	Shungin	No
rs3902751	7	25,828,164	A	G	0.250	0.023	0.004	8.74e-10	WHR	Shungin	Yes
rs7801581	7	27,190,296	T	C	0.244	0.023	0.004	4.95e-08	WHR	Shungin	Yes
rs12679556	8	72,676,782	G	T	0.247	0.024	0.004	1.16e-09	WHR	Shungin	No
rs10842707	12	26,362,631	T	C	0.232	0.027	0.004	1.39e-11	WHR	Shungin	No
rs1443512	12	52,628,951	A	C	0.237	0.026	0.004	2.76e-11	WHR	Shungin	No
rs10783615	12	52,636,040	G	A	0.145	0.035	0.005	7.02e-13	WHR	Shungin	Yes
rs2071449	12	52,714,278	A	C	0.369	0.025	0.004	3.85e-12	WHR	Shungin	Yes
rs1440372	15	64,820,205	C	T	0.710	0.021	0.004	7.59e-09	WHR	Shungin	No

rs4081724	19	38,516,786	G	A	0.851	0.028	0.005	1.51e-08	WHR	Shungin	No
rs2294239	22	27,779,477	A	G	0.586	0.020	0.003	4.39e-09	WHR	Shungin	No

F-statistics

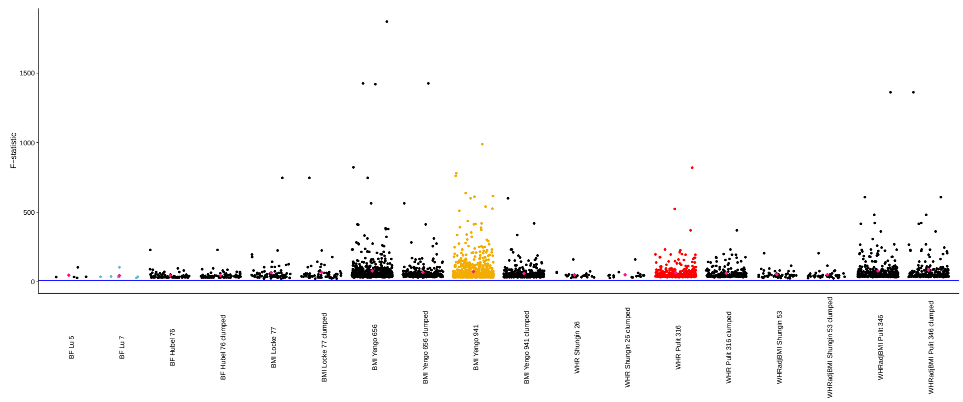

Figure A.8: f-statistics for all exposures used in chapter 5

Mean f-statistic for each exposure indicated by the pink diamond. The blue line indicates a nominal threshold of 10. Exposures used in the main analysis are highlighted with coloured points. The name after each exposure trait represents the authors last name of the original GWAS publication for which each exposure was obtained. The number following the first authors last name represents the number of SNPs obtained from the original GWAS and included; clumped refers to this original number of SNPs having been pruned based on an LD R^2 of 0.001. *BMI = body mass index, WHR = wasit hip ratio, WHRadjBMI = wasit hip ratio adjusted for BMI, BF = body fat percentage.*

Correlations

Consistency in effect direction and size was investigated using Spearman's correlations.

```
[1] "Correlations between exposures"

                BF_Lu_7 BMI_Yengo_941 WHR_Pulit_316
BF_Lu_7        1.0000000    -0.7012485    -0.7189189
BMI_Yengo_941 -0.7012485     1.0000000     0.9449575
WHR_Pulit_316 -0.7189189     0.9449575     1.0000000
```

Sensitivity analysis

Method comparison For all method comparison Circos plots the outer track is the main analysis (IVW-MRE) result, and is coloured for the exposure for consistency with the main text of the thesis (BMI = yellow, WHR = red, BF = blue). Purple = MR Egger, green = Weighted median, orange = Weighted mode. Solid points represent a *p-value* threshold of $0.05/22$ having been met; however only directional consistency between the methods is of interest when comparing the IVW-MRE model to the sensitivity models.

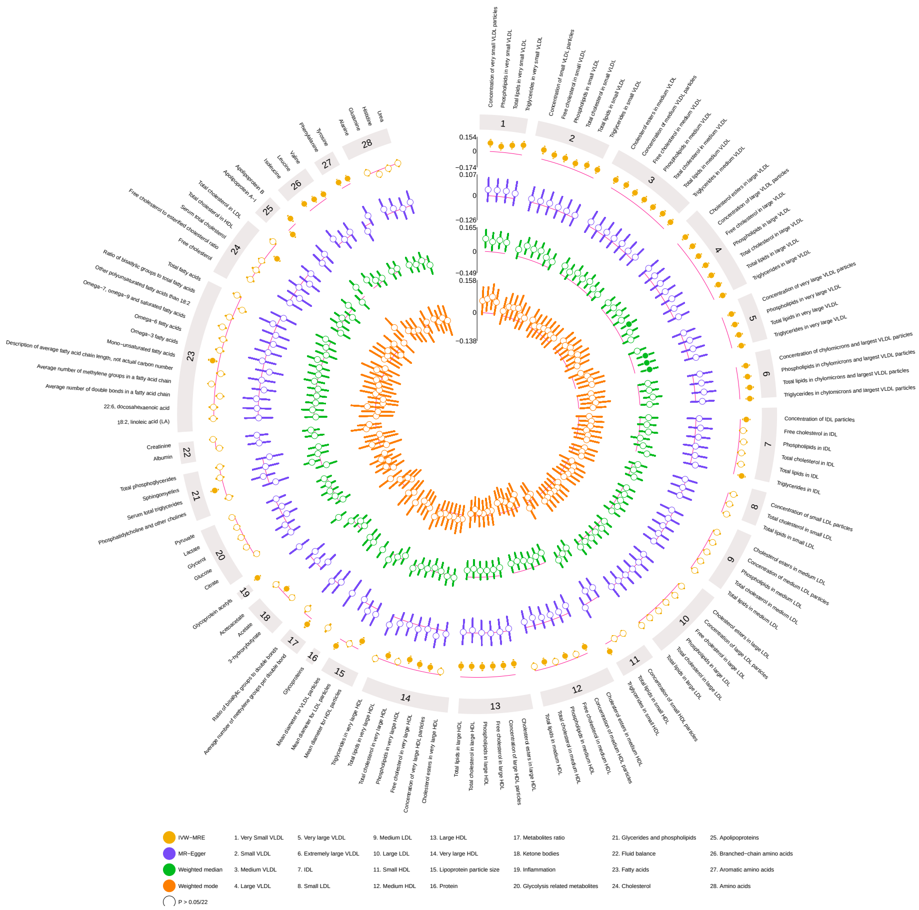

Figure A.9: Circosplot of main and sensitivity analysis for BMI

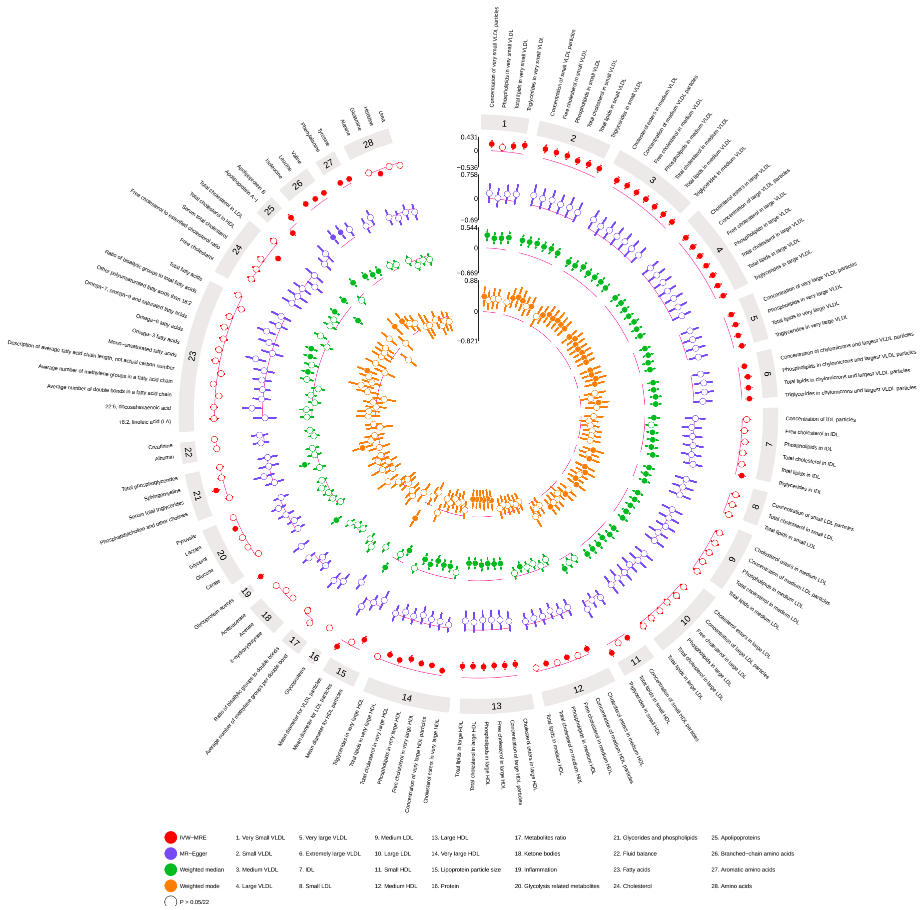

Figure A.10: Circosplot of main and sensitivity analysis for WHR

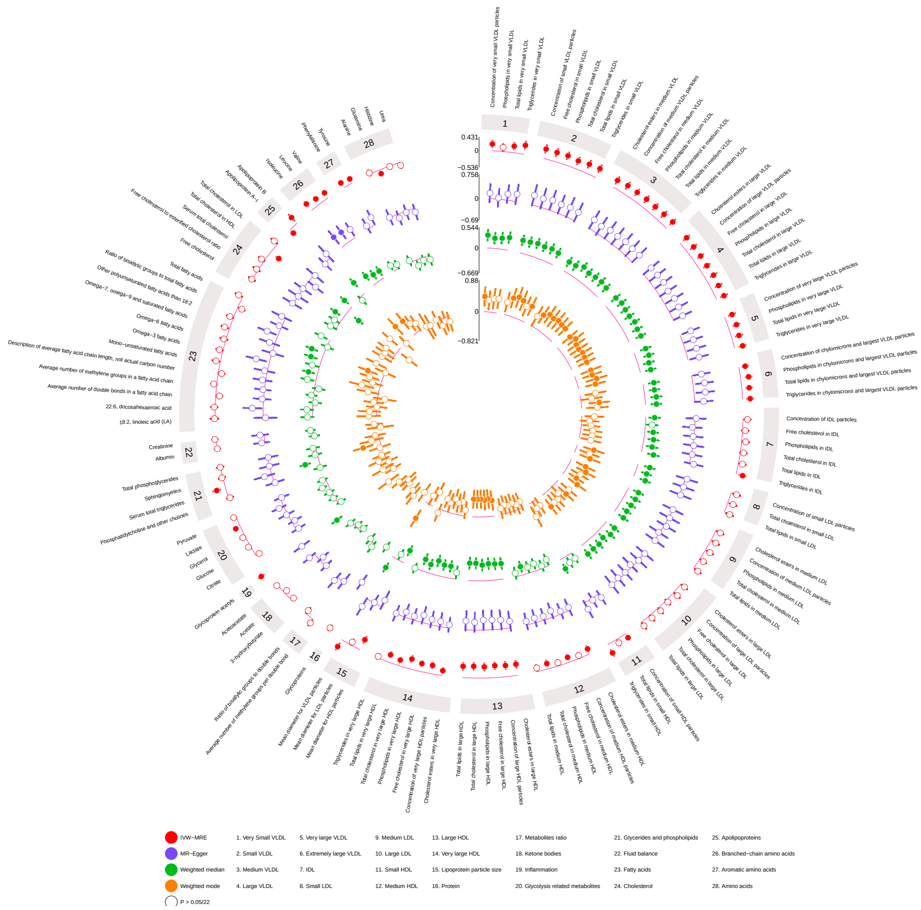

Figure A.11: Circosplot of main and sensitivity analysis for BF

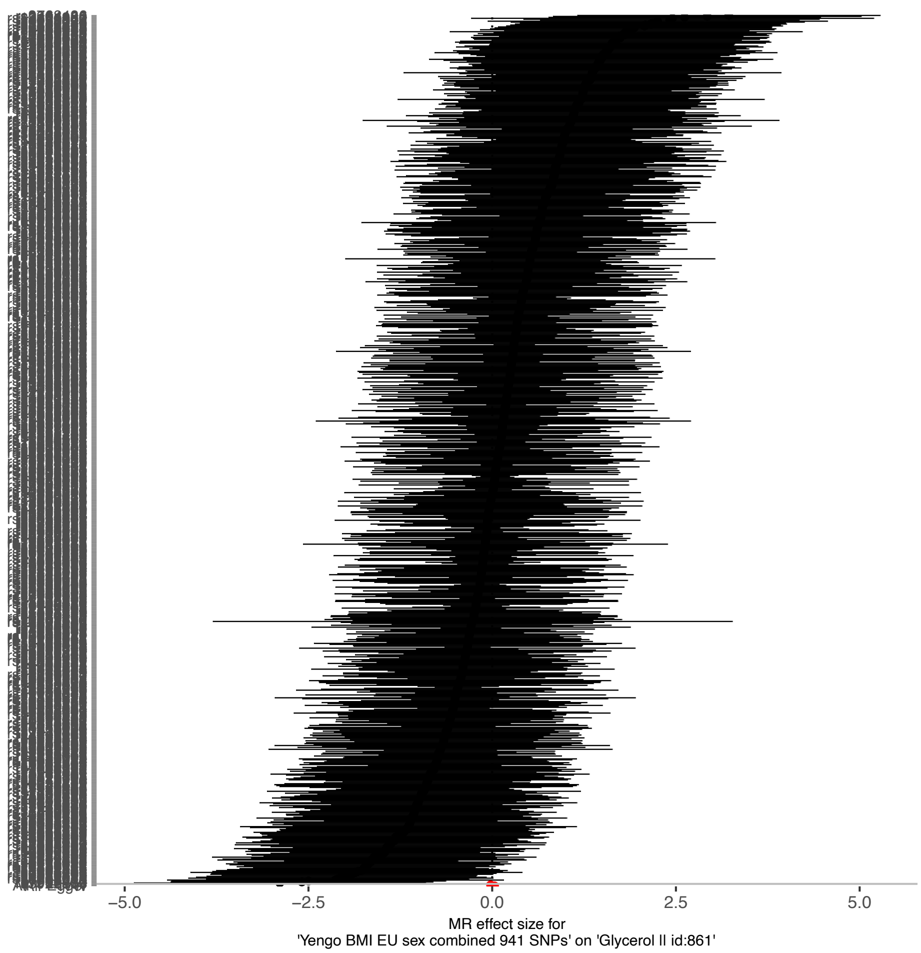

Figure A.12: Single SNP MR results for BMI and glycerol - representative figure

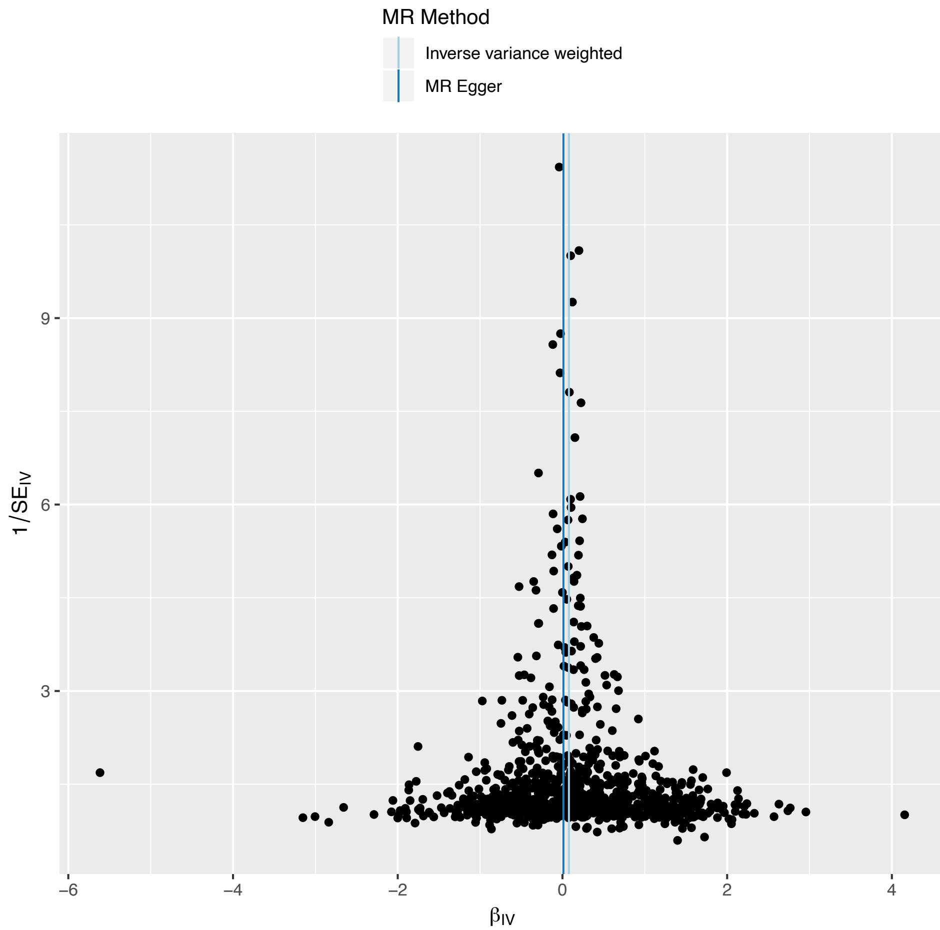

Figure A.13: Funnel plot of single SNP MR results for BMI and Apolipoprotein B - representative figure

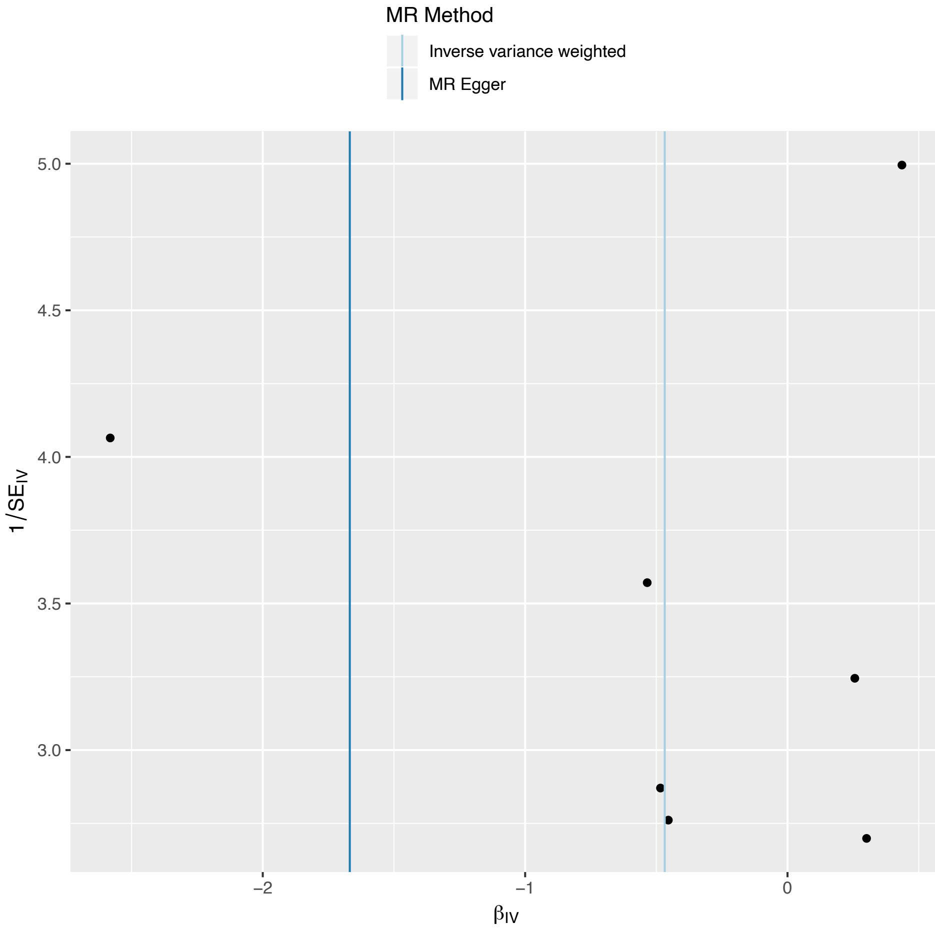

Figure A.14: Funnel plot of single SNP MR results for BF and Apolipoprotein B - representative figure

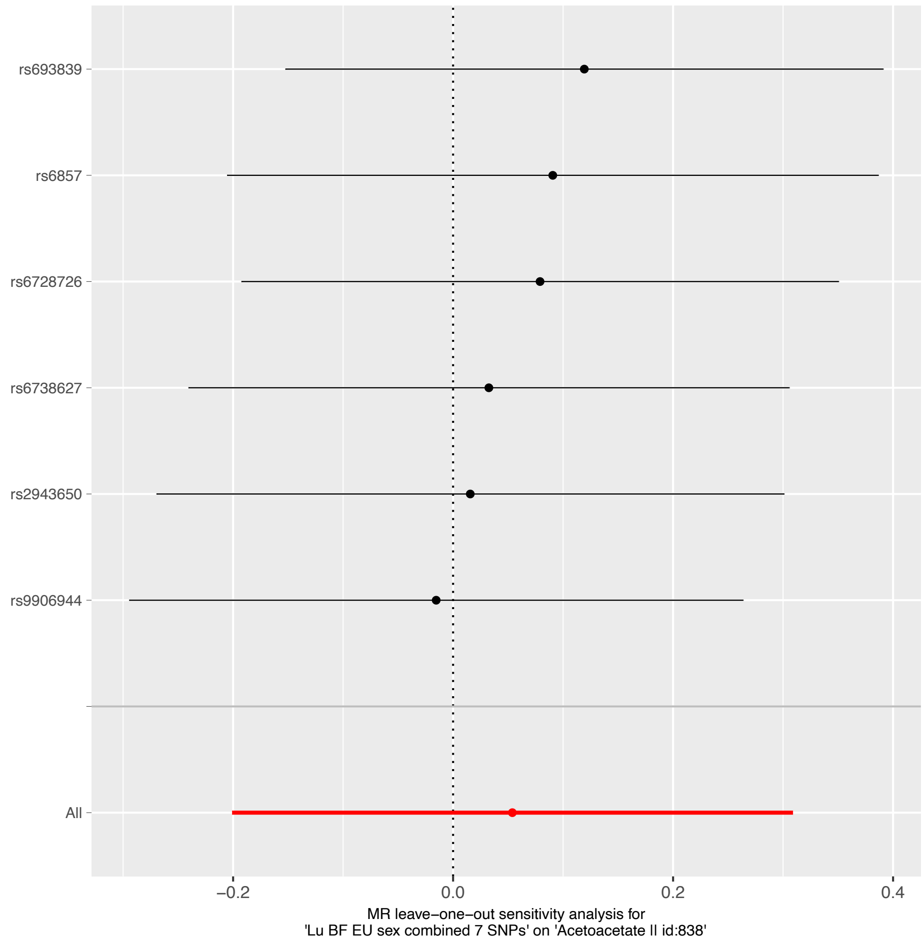

Figure A.15: Leave-one-iut results for BF and Acetoacetate - representative figure

Figure A.16: Leave-one-iut results for BMI and Acetate - representative figure

Representative figures

A.6 Chapter 6

Appendix B

This first appendix includes all of the R chunks of code that were hidden throughout the document (using the `include = FALSE` chunk tag) to help with readibility and/or setup.

In the main Rmd file

This thesis was created using R Markdown. The template used here I have adapted from the R Markdown template here (`https://github.com/ismayc/thesisdown`), which is adapted from the Markdown template (`https://github.com/matlipson/phd_thesis_markdown`), which is an extension of Tom Pollards original Markdown for thesis work (`https://github.com/tompollard/phd_thesis_markdown`).

Appendix C

Appendix B contains all of the code used throughout the thesis that is hidden from the reader using the `include = FALSE` chunk tag. This code is not necessary for reading, but is included here for completeness and transparency, and consists mainly of package installs and code to produce tables and figures included in the text.

To create the finished thesis file in R Markdown an index.Rmd file is used to compile multiple .Rmd files together. The index.Rmd file contains the YAML header, along with the following R code that installs and loads the neccessary packages to compile the thesis:

```
doc.type <- knitr::opts_knit$get('rmarkdown.pandoc.to')
source("data/index/packages.R")
```

C.1 Code from Chapter 1

C.2 Code from Chapter 2

C.3 Code from Chapter 3

C.4 Code from Chapter 4

C.5 Code from Chapter 5

C.6 Code from Chapter 6

C.7 Code from Chapter 7

C.8 Code from Chapter 8

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Abbreviations

“‘{r abbreviations, include=FALSE, echo=FALSE, cache=TRUE} library(tidyverse) library(knitr)

data_frame(Term = c(“Mendelian randomization”, “Single nucleotide polymorphism”), Abbreviation = c(“MR”, “SNP”)) %>% arrange(Term) %>% # i.e. alphabetical order by Term kable(booktab = T) # booktab = T gives us a pretty APA-ish table “‘

MR - Mendelian randomization

SNP - Single nucleotide polymorphism